REFLECT RESET RECHARGE: PRECISION MEDICINE-PHARMACOGENOMICS OVERVIEW

Natasha Petry, PharmD, MPH, BCACP

Pharmacogenomics Pharmacist

Sanford Imagenetics

Associate Professor

North Dakota State University

OBJECTIVES:

1. Define pharmacogenomics (PGx)
2. Describe how pharmacogenomics is used in patient care
3. List resources to aid in the use of PGx results

SANFORD imagenetics

WHAT IS PHARMACOGENOMICS?

PHARMACOLOGY TAKING INTO CONSIDERATION HOW GENETIC FACTORS EFFECT A PATIENTS REACTIONS TO MEDICATIONS

***The study of medication response in relation to the genome**

PHARMACY + GENOMICS

Pharmacogenomics is the study of how genes affect a person's response to drugs.

This field combines pharmacology and genomics to develop effective, safe medications that can be prescribed based on a person's genetic makeup.

https://medlineplus.gov/genetics/understanding/genomicresearch/pharmacogenomics/

SCIENCE OF MEDICATIONS

+

STUDY OF GENES AND THEIR FUNCTIONS

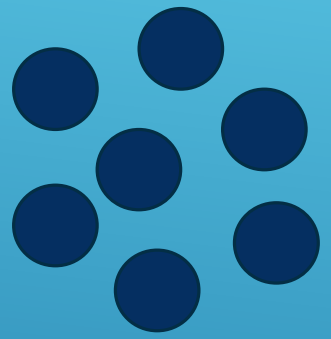
=

Pharmacogenomics

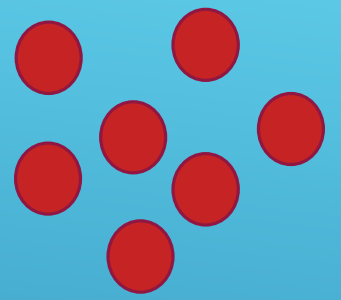
BENEFITS OF PGX TESTING

- **Drug safety/toxicity avoidance**
  - Aid drug selection to avoid adverse reactions
  - Aid dose selection to avoid toxicity
- **Increased efficacy**
  - Aid dose selection for maximum efficacy
  - Identify patients who should be responsive to a given drug

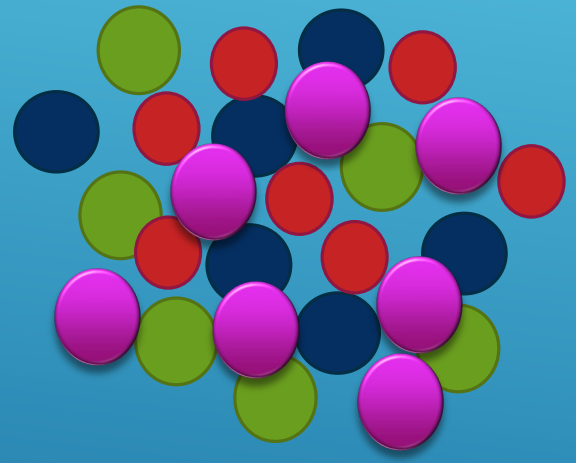
Drug not toxic and not beneficial



Drug not toxic but BENEFICIAL

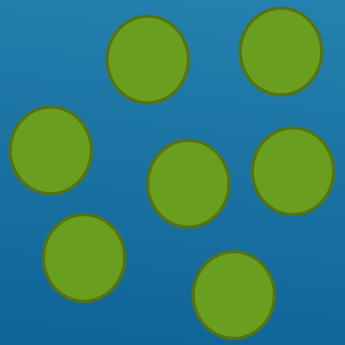


Patient group

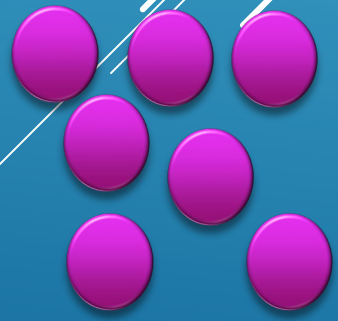


Same diagnosis
Receive same prescription

Drug TOXIC but BENEFICIAL



Drug TOXIC but not beneficial



Other factors play a role as well: genetics, age, ethnicity, weight, gender, medications, diet, other conditions

CAUTION

- Consider use evidence-based information, literature and guidelines
- Actionable

  What if clinical picture is controlled?

- What is not helpful for right now?
  - May report many results but may not be evidence backing change in therapy

LIMITATIONS

Targeted testing

- not whole genome = not comprehensive
- Variation between labs/companies

May not always be a clear answer on what to do

- May be no intervention
- Different tests report different genes/alleles

Can be expensive

Only a piece of the puzzle

- Not all drug responses due to genetics

UTILITY

- Not all medications have PGx recommendations
- Important to know evidence
- Research where results are from

INSURANCE

- Panel - generally not covered (exceptions)
- Single gene tests –potentially covered depending on the insurance, gene tested, and patient clinical profile
- Flex spending account - depends on their insurance
- Recommend patients contact their insurance and/or flex spending prior to testing if cost an issue

PREEMPTIVE TESTING

- Screening for variants
- Test results available at time of prescribing
- Usually panels

REACTIVE TESTING

- Ordered in response to lack of efficacy or side effects
- Ordered in anticipation of beginning certain therapies
- Usually single gene
  - Panels often used for reactive depression/anxiety

Pharmacokinetics (Pk)

What the body does to the drug

Absorption

Distribution

→ IN

Metabolism

Elimination

→ OUT

ACTIVE DRUGS - BIOLOGICALLY ACTIVE

- Absorbed thru GI tract
- Distributed in the blood
- Broken down by liver enzymes
- Excreted by the kidneys

PRODRUGS – BIOLOGICALLY INACTIVE DRUG

- Require biological activation
  - Improve drug delivery or specificity
  - Improve bioavailability
  - Decrease toxicity
  - Cytochrome P450 enzymes (CYP2C19, CYP2D6, etc.)
    - Genetic variants in CYP enzymes
    - Ex. Codeine > Morphine

Pharmacogenomic Enzyme Variants

- Genetics variants in metabolizing enzymes and drug transporters that cause changes in drug metabolism: Insertions, Deletions, Inversions, Translocation

- Assignment of phenotype and functional affect: depends on active or prodrug

- Healthcare professionals (MD, PhD, Pharm. D.)
- International Consortium to facilitate the use of Pgx tests for patient care
- Provide guidelines for actionable prescribing decisions from genetic test translation
- Create clinical practice guidelines based on peer reviewed, evidence based, updatable information
- Standardized format for terminology, evidence grading and clinical recommendations
- Published in Clinical Pharmacology and Therapeutics
- Dutch Pharmacogenetics Working Group, Canadian Pharmacogenomics Network for Drug Safety, and European Pharmacogenetics Implementation Consortium

https://cpicpgx.org

SunTrust Online Bank | Living Well - St. Jude | Altmetric it! | Big Brother Junkies - | CoreSource ICE Porta

CPIC | Guidelines | Genes-Drugs | Alleles | Publications | Meetings | Resources | Informatics | Members | Contact

CPIC guidelines and list of CPIC genes/drugs

CPIC®
Clinical Pharmacogenetics Implementation Consortium

CPIC information

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.

LEVELS OF EVIDENCE

CPIC assigns levels to the evidence linking genotype to phenotype. The literature-based evidence summarized in each guideline's supplement is graded[1] on a scale of high, moderate and weak, defined as follows:

High: Evidence includes consistent results from well-designed, well-conducted studies.

Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence.

Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

[1] Valdes R, Payne DA, Linder MW. Laboratory analysis and application of pharmacogenetics to clinical practice. The National Academy of Clinical Biochemistry (NACB) – Laboratory Medicine Practice Guidelines. Washington, DC2010.

NOTABLE CPIC DRUG-GENE PAIRS

- *TPMT and NUDT15*
  - Mercaptopurine, thioguanine, azathioprine
- *CYP2D6*
  - Codeine, tramadol, hydrocodone, oxycodone, tamoxifen, fluvoxamine, paroxetine, amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, trimipramine, ondansetron, tropisetron, atomoxetine
- *CYP2C19*
  - Escitalopram, citalopram, sertraline, amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, trimipramine, clopidogrel, voriconazole, omeprazole, lansoprazole, pantoprazole, dexlansoprazole
- *VKORC1*
  - Warfarin
- *CYP2C9*
  - Aspirin, diclofenac, celecoxib, flurbiprofen, aceclofenac, ibuprofen, indomethacin, lornoxicam, lumiracoxib, meloxicam, metamizole, nabumetine, naproxen, piroxicam, tenoxicam, warfarin, phenytoin
- *CYP4F2*
  - Warfarin
- *HLA-A*
  - Carbemazepine, oxcarbazepine
- *HLA-B*
  - Allopurinol, abacavir, phenytoin, oxcarbazepine, carbamazepine
- *CFTR*
  - Ivacaftor

CPIC DRUG-GENE PAIRS (CONT.)

- *DPYD*
  - fluorauracil, capecitabine, tegafur
- *G6PD*
  - Rasburicase
- *UGT1A1*
  - Atazanavir
- *SLCO1B1*
  - Statins
- *IFNL3 (IL28B)*
  - Peginterferon alfa-2a, peginterferon alfa-2b, ribavirin
- *CYP3A5*
  - Tacrolimus
- *CYP2B6*
  - Efavirenz
- *RYR1 and CACNA1S*
  - Desflurane, enflurane, halothane, isoflurane, methoxyflurane, sevoflurane, succinylcholine

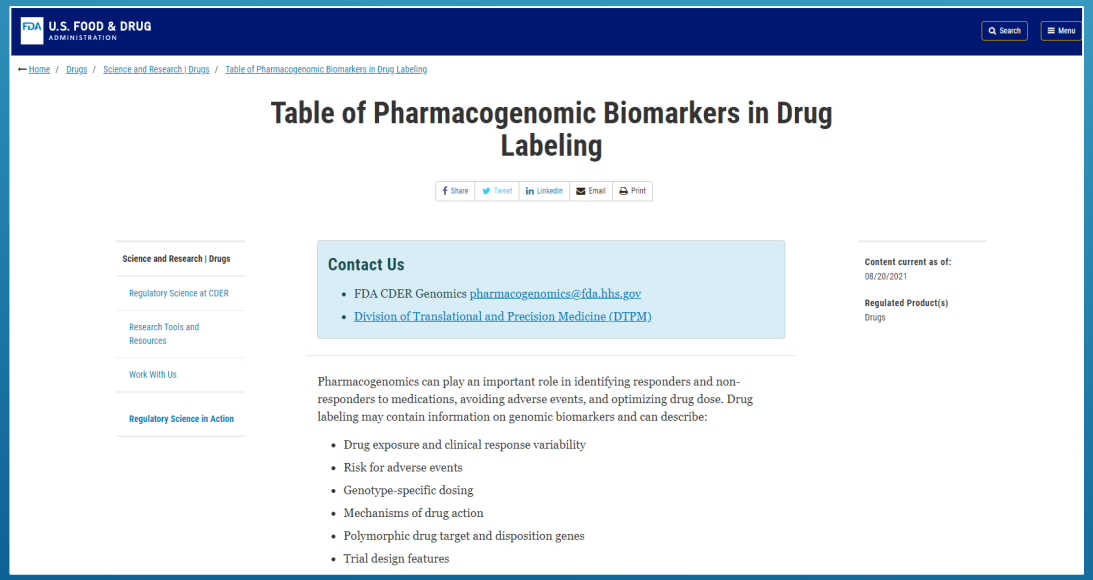
DUTCH PHARMACOGENETICS WORKING GROUP (DPWG)

- Established in 2005
- Recommendations have been developed for over 80 drugs and are updated every 3 months
- https://www.knmp.nl/patientenzorg/medicatiebewaking/farmacogenetica/pharmacogenetics-1/pharmacogenetics

FDA PHARMACOGENOMIC RESOURCES

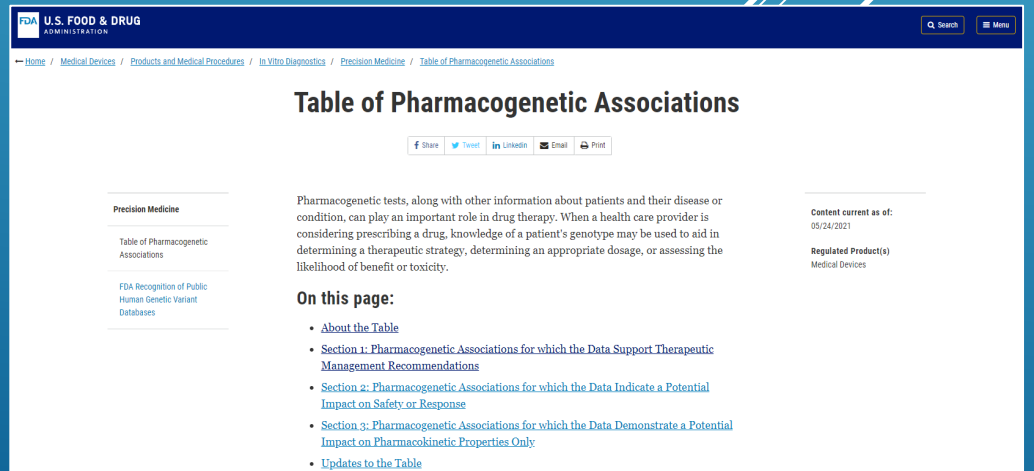
FDA Table of Pharmacogenomic Biomarkers in Drug Labeling

- Contains genetic information contained on drug labeling
- Search function available



FDA Table of Pharmacogenetic Associations

- Lists gene-drug interactions
- FDA may or may not advocate for a pharmacogenetic test with the corresponding medication
- Divided into 3 Sections on Pharmacogenetic Associations:
  - 1. Data Supports Therapeutic Management Recommendations
  - 2. Data Indicates a Potential Impact on Safety or Response
  - 3. Data Demonstrates a Potential Impact on Pharmacokinetic Properties Only



PART OF THE TABLE OF PGX BIOMARKERS

FDA.GOV

Download detailed version of the Table of Pharmacogenomic Biomarkers in Drug Labeling with Labeling Text (PDF - 2.6MB)

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
Alglucosidase Alfa	Inborn Errors of Metabolism	GAA	Warnings and Precautions
Alpelisib (1)	Oncology	ERBB2 (HER2)	Indication and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies
Alpelisib (2)	Oncology	ESR (Hormone Receptor)	Indication and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies
Alpelisib (3)	Oncology	PIK3CA	Indication and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies
Amifampridine	Neurology	NAT2	Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology
Amifampridine Phosphate	Neurology	NAT2	Dosage and Administration, Use in Specific Populations, Clinical Pharmacology
Amitriptyline	Psychiatry	CYP2D6	Precautions
Amoxapine	Psychiatry	CYP2D6	Precautions

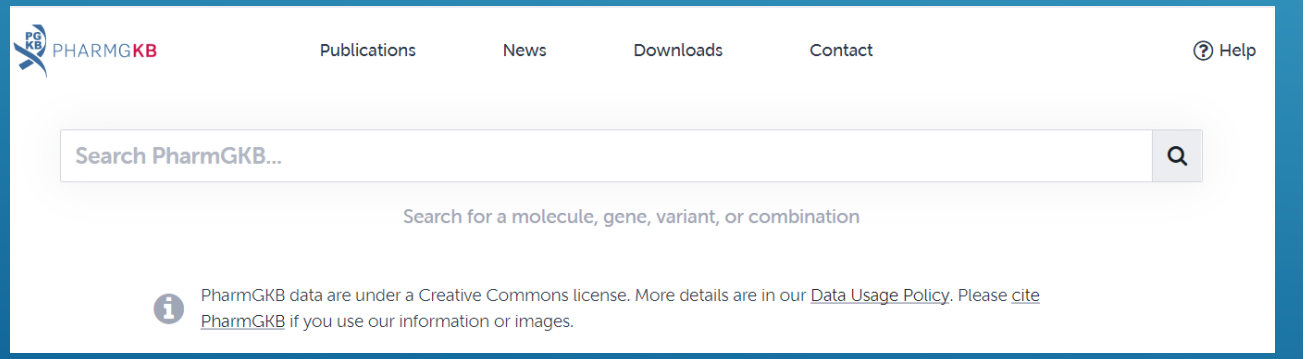
TABLE OF PGX ASSOCIATIONS

Section 1: Pharmacogenetic Associations for which the Data Support Therapeutic Management Recommendations

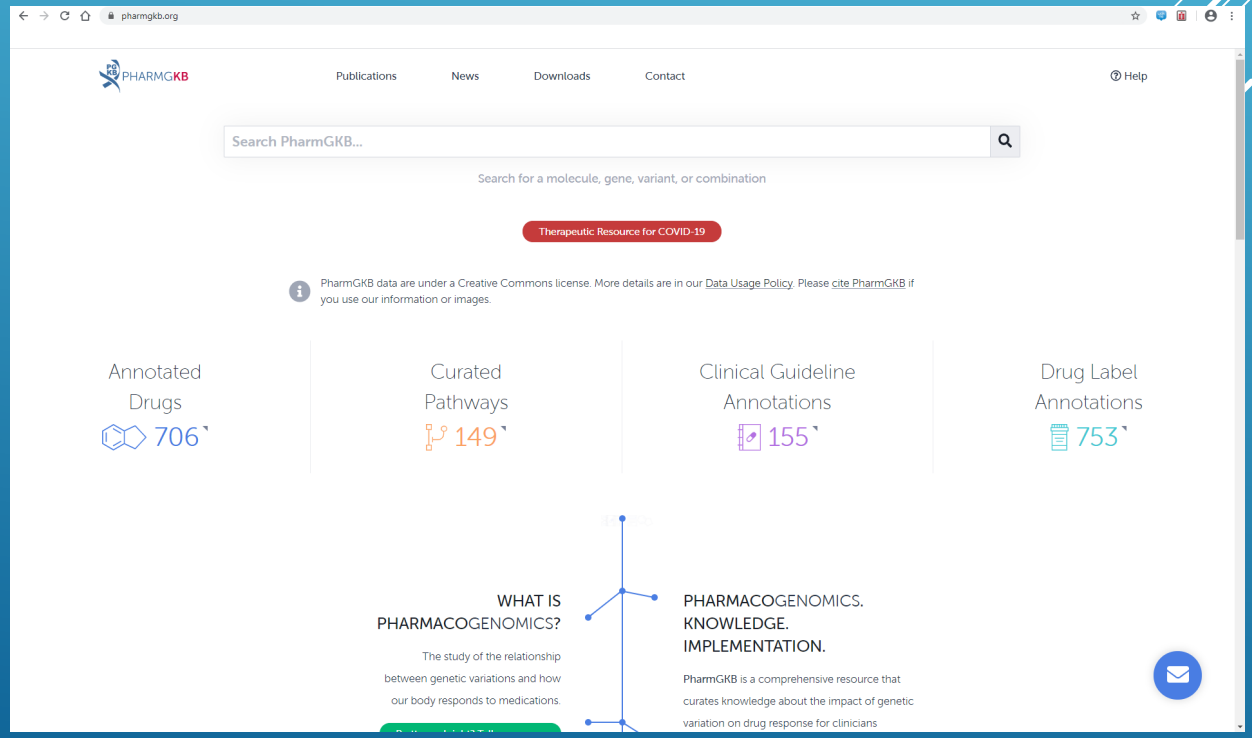
Drug	Gene	Affected Subgroups+	Description of Gene-Drug Interaction
Abacavir	HLA-B	*57:01 allele positive	Results in higher adverse reaction risk (hypersensitivity reactions). Do not use abacavir in patients positive for HLA-B*57:01.
Amifampridine	NAT2	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk. Use lowest recommended starting dosage and monitor for adverse reactions. Refer to FDA labeling for specific dosing recommendations.
Amifampridine Phosphate	NAT2	poor metabolizers	Results in higher systemic concentrations. Use lowest recommended starting dosage (15 mg/day) and monitor for adverse reactions.
Amphetamine	CYP2D6	poor metabolizers	May affect systemic concentrations and adverse reaction risk. Consider lower starting dosage or use alternative agent.
Aripiprazole	CYP2D6	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk. Dosage adjustment is recommended. Refer to FDA labeling for specific dosing recommendations.
Aripiprazole Lauroxil	CYP2D6	poor metabolizers	Results in higher systemic concentrations. Dosage adjustment is recommended. Refer to FDA labeling for specific dosing recommendations.
Atomoxetine	CYP2D6	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk. Adjust titration interval and increase dosage if tolerated. Refer to FDA labeling for specific dosing recommendations.
Azathioprine	TPMT and/or NUDT15	intermediate or poor metabolizers	Alters systemic active metabolite concentration and dosage requirements. Results in higher adverse reaction risk (myelosuppression). Consider alternative therapy in poor metabolizers. Dosage reduction is recommended in intermediate metabolizers for NUDT15 or TPMT. Intermediate metabolizers for both genes may require more substantial dosage reductions. Refer to FDA labeling for specific dosing recommendations.
Belinostat	UGT1A1	*28/*28 (poor metabolizers)	May result in higher systemic concentrations and higher adverse reaction risk. Reduce starting dose to 750 mg/m2 in poor metabolizers.

PHARMGKB

- PharmGKB is a resource that can guide you to various sources and guidelines for drug-gene interactions
- It is a collection of common drug-gene guidelines including CPIC, DPWG, FDA, and more
  - Less commonly used guidelines found on PharmGKB include Swiss, Canadian, and European guidelines
- www.pharmgkb.org



Search by drug or gene



MAPPING OF DATA

Gene	Allele/Haplotype Tagging SNP(s)	Polymorphism	dbSNP ID	Predicted Effect on Protein
CYP2C19	*5	90033C>T	rs56337013	R433W
CYP2C19	*6	12748G>A	rs72552267	R132Q
CYP2C19	*7	19294T>A	rs72558186	Splicing defect
CYP2C19	*8	12711T>C	rs41291556	W120R
CYP2C19	*9	12784G>A	rs17884712	R144H
CYP2C19	*10	19153C>T	rs6413438	P227L
CYP2C19	*11	12802G>A	rs58973490	R150H
CYP2C19	*12	90209A>C	rs55640102	X491C, 26 extra aa
CYP2C19	*13	87290C>T	rs17879685	R410C
CYP2C19	*14	50T>C	rs55752064	L17P
CYP2C19	*15	55A>C	rs17882687	I19L
CYP2C19	*16	90060C>T	rs192154563	R442C
CYP2C19	*17	-806C>T	rs12248560	Increased expression
CYP2C19	n/a	-806C>T, c.463G>T	2248560, rs3740369	-, E155X
CYP2C19	*18	80156G>A, 87106T>C	138142612,rs491762	R329H, -
CYP2C19	*19	151A>G, 87106T>C	-, rs4917623	S51G, -
CYP2C19	*22	17869G>C	rs140278421	R186P
CYP2C19	*23	12455G>C	rs118203756	G91R
CYP2C19	*24	80174G>A, 87259A>G	rs118203757, -	R335Q, -
CYP2C19	*25	90080C>G	rs118203759	F448L
CYP2C19	*26	19239G>A	-	D256N
CYP2C19	*27	-1041G>A	-	-
CYP2C19	*28	T, -2020C>A, -1439T>C, 55A>C, 80	789, rs17878739, rs1	-, -, -, I19L, V374I
CYP2C19	*29	83A>T	-	K28I
CYP2C19	*30	12401C>T g	rs145328984	R73C
CYP2C19	*31	12416C>T	-	H78Y
CYP2C19	*32	12480A>G	-	H99R
CYP2C19	*33	17874G>A	rs370803989	D188N
CYP2C19	*34	-13G>A, 7C>T, 10T>C	367543002, rs36754	-, P3S, F4L

CYP2C19 *2/*2	PM	Poor Metabolizer
CYP2C19 *2/*3	PM	Poor Metabolizer
CYP2C19 *2/*4	PM	Poor Metabolizer
CYP2C19 *2/*5	PM	Poor Metabolizer
CYP2C19 *2/*6	PM	Poor Metabolizer
CYP2C19 *2/*7	PM	Poor Metabolizer
CYP2C19 *2/*8	PM	Poor Metabolizer

CREATING GUIDELINES

Table 1 Assignment of likely CYP2C19 phenotypes based on genotypes

Likely phenotype	Genotypes	Examples of diplotypes
Ultrarapid metabolizer: normal or increased activity (~5–30% of patients)	An individual carrying two increased activity alleles (*17) or one functional allele (*1) plus one increased-activity allele (*17)	*1/*17, *17/*17
Extensive metabolizer: homozygous wild-type or normal activity (~35–50% of patients)	An individual carrying two functional (*1) alleles	*1/*1
Intermediate metabolizer: heterozygote or intermediate activity (~18–45% of patients)	An individual carrying one functional allele (*1) plus one loss-of-function allele (*2–*8) or one loss-of-function allele (*2–*8) plus one increased-activity allele (*17)	*1/*2, *1/*3, *2/*17
Poor metabolizer: homozygous variant, mutant, low, or deficient activity (~2–15% of patients)	An individual carrying two loss-of-function alleles (*2–*8)	*2/*2, *2/*3, *3/*3

Some rare genotype combinations have unclear predicted metabolic phenotypes; see **Supplementary Table S5** online.

Table 2 Antiplatelet therapy recommendations based on CYP2C19 status when considering clopidogrel for ACS/PCI patients

Phenotype (genotype)	Implications for clopidogrel	Therapeutic recommendations	Classification of recommendations[a]
Ultrarapid metabolizer (UM) (*1/*17, *17/*17) and extensive metabolizer (EM) (*1/*1)	Normal (EM) or increased (UM) platelet inhibition; normal (EM) or decreased (UM) residual platelet aggregation[b]	Clopidogrel: label-recommended dosage and administration	Strong
Intermediate metabolizer (*1/*2, *1/*3, *2/*17)	Reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events	Alternative antiplatelet therapy (if no contraindication), e.g., prasugrel, ticagrelor	Moderate
Poor metabolizer (*2/*2, *2/*3, *3/*3)	Significantly reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events	Alternative antiplatelet therapy (if no contraindication), e.g., prasugrel, ticagrelor	Strong

[a]See **Supplementary Materials and Methods** (Strength of Therapeutic Recommendations) online. [b]The *CYP2C19*17* allele may be associated with increased bleeding risks (ref. 15). ACS, acute coronary syndrome; PCI, percutaneous coronary intervention.

SUPPLEMENTAL TABLE S1. ASSOCIATION BETWEEN ALLELIC VARIANTS[A] AND CYP2D6 ENZYME ACTIVITY

Functional Status (10, 15)	Activity Value[c,d]	Alleles
Increased function	>1	*1xN, *2xN, *35xN, *45xN
Normal or Increased function	1 or >1[h]	*9xN, *10xN, *17xN, *29xN, *41xN
Normal function[b]	1	*1[e], *2, *27, *33, *34[f], *35, *39[f], *45[g], *46[g], *48, *53
Decreased function	0.5	*9, *10, *14B,*17, *29, *41, *49, *50, *54, *55, *59, *72
No function	0	*3, *3xN, *4, *4xN, *5, *6, *6xN, *7, *8, *11, *12, *13, *14A, *15, *18, *19, *20, *21, *31, *36, *36xN, *38, *40, *42, *44, *47, *51, *56, *57, *62,*68, *69, *92, *100, *101
Unknown	N/A	*22, *23, *24, *25, *26, *28, *30, *32, *37, *43, *43xN, *52, *58, *60, *61, *63, *64, *65, *70, *71, *73, *74, *75, *81, *82, *83, *84, *85, *86, *87, *88, *89, *90, *91, *93, *94, *95, *96, *97, *98, *102, *103, *104, *105, *107, *108, *109

[a]See http://www.cypalleles.ki.se/cyp2d6.htm and the *CYP2D6* Allele Definition Table (7) for updates on *CYP2D6* allelic variants and nomenclature.

SUPPLEMENTAL TABLE S2. EXAMPLES OF *CYP2D6* GENOTYPES WITH RESULTING ACTIVITY SCORES AND PHENOTYPE CLASSIFICATION

Allele 1	Allele 2	*CYP2D6* Diplotype	CYP2D6 Activity Score[a]	Phenotype
*1	*1xN[b]	*1/*1xN	≥3.0	UM
*2x2[c]	*41	*2x2/*41	2.5	UM
*1	*2	*1/*2	2.0	NM
*1	*17	*1/*17	1.5	NM
*2	*3	*2/*3	1.0	NM
*1	*4x2[d]	*1/*4x2	1.0	NM
*10	*10	*10/*10[e]	1.0	NM[e]
*4[d]	*10	*4/*10	0.5	IM
*5	*6	*5/*6[f]	0	PM

Abbreviations are as follows: NM = normal metabolizer, IM = intermediate metabolizer, PM =

PROCESS AND REPORTING

- Ordered entered into Electronic Medical Record
- Blood drawn and sent to molecular lab for testing
- Genotyping results validated by lab director(s)
- Phenotyping/functional status validated by pharmacist(s)
  - Patient chart review

Basic PharmGx Panel

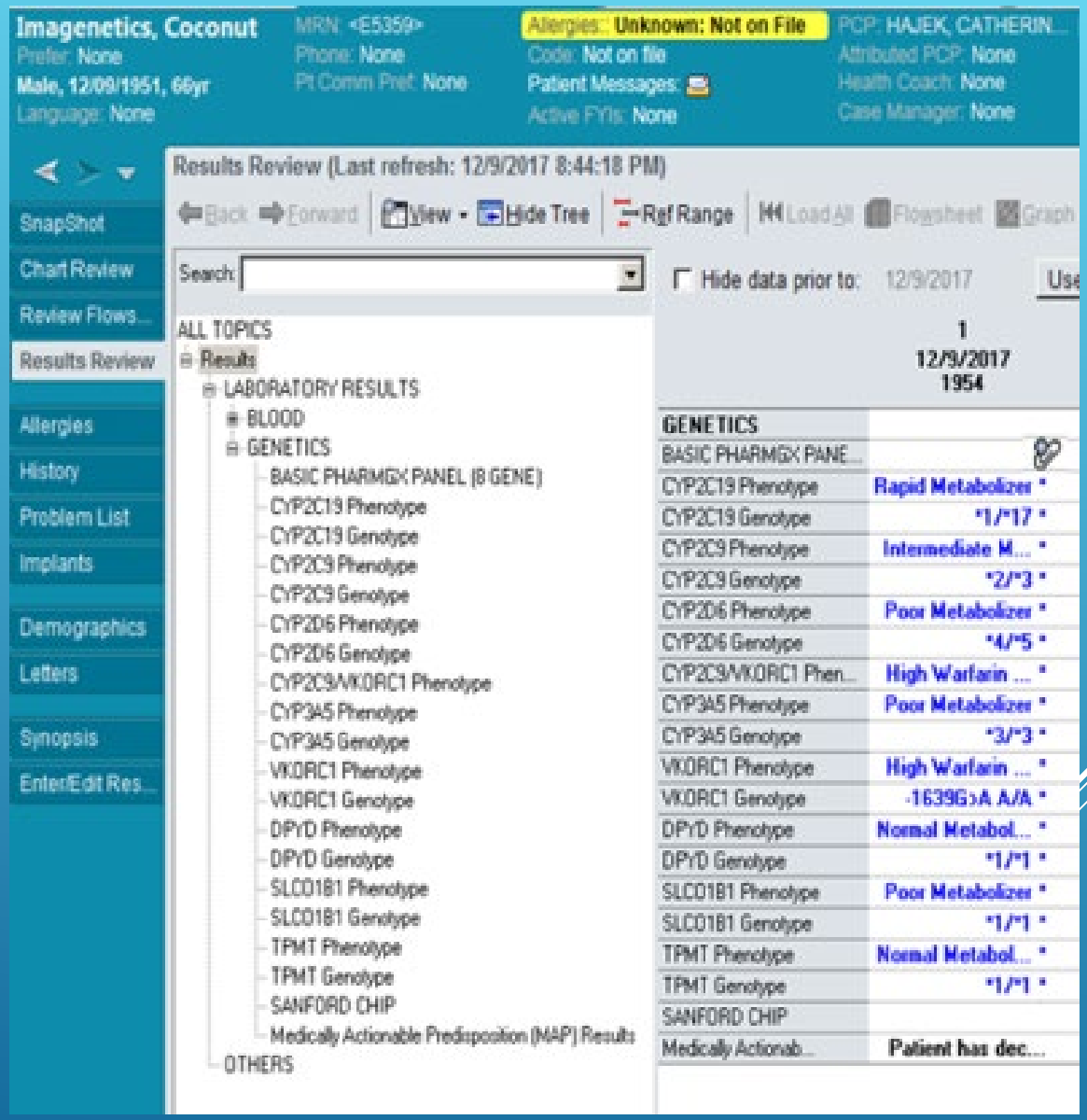
Res	Component	Value	Units	!	Δ	L	IE	R	Ref. Range	Method	Chart	PV
1	TPMT GENOTYPE	*1/*3C								MOLECULAR GENETICS MG		
1	CYP2C9 GENOTYPE	*1/*1								MOLECULAR GENETICS MG		
1	CYP2C19 GENOTYPE	*1/*2								MOLECULAR GENETICS MG		
1	CYP2D6 GENOTYPE	*2/*4								MOLECULAR GENETICS MG		
1	CYP3A5 GENOTYPE	*3/*3								MOLECULAR GENETICS MG		
1	VKORC1 GENOTYPE	-1639G>A G/A								MOLECULAR GENETICS MG		
1	DPYD GENOTYPE	*1/*1								MOLECULAR GENETICS MG		
1	SLCO1B1 GENOTYPE	*5/*5								MOLECULAR GENETICS MG		
1	TPMT PHENOTYPE	Intermediate Metabolizer								MOLECULAR GENETICS MG		
1	CYP2C9 PHENOTYPE	Normal Metabolizer								MOLECULAR GENETICS MG		
1	CYP2C19 PHENOTYPE	Intermediate Metabolizer								MOLECULAR GENETICS MG		
1	CYP2D6 PHENOTYPE	Normal Metabolizer								MOLECULAR GENETICS MG		
1	CYP3A5 PHENOTYPE	Poor Metabolizer								MOLECULAR GENETICS MG		
1	VKORC1 PHENOTYPE	Intermediate Warfarin Sensitivity								MOLECULAR GENETICS MG		
1	DPYD PHENOTYPE	Normal Metabolizer								MOLECULAR GENETICS MG		
1	SLCO1B1 PHENOTYPE	Poor Function								MOLECULAR GENETICS MG		
1	CYP2C9/VKORC1 PHENOTYPE	Low Warfarin Sensitivity								MOLECULAR GENETICS MG		

Result comments:

Complete interpretive report under separate document.

Method: MOLECULAR GENETICS MG Last received: 3/19/2018 0957 Last verified: 3/25/2018 1402 by Reiner, Jennifer, PHD

RETURN OF RESULTS



PHENOTYPES

Term	Functional definition	Genetic definition
Ultrarapid metabolizer	Increased enzyme activity compared to rapid metabolizers	2 increased function alleles, or more than 2 normal function alleles
Rapid metabolizer	Increased enzyme activity compared to normal metabolizers but less than ultrarapid metabolizers	Combinations of normal function and increased function alleles
Normal metabolizer	Fully functional enzyme activity	Combinations of normal function and decreased function alleles
Intermediate metabolizer	Decreased enzyme activity (activity between normal and poor metabolizer)	Combinations of normal function, decreased function, and/or no function alleles
Poor metabolizer	Little to no enzyme activity	Combination of no function alleles and/or decreased function alleles

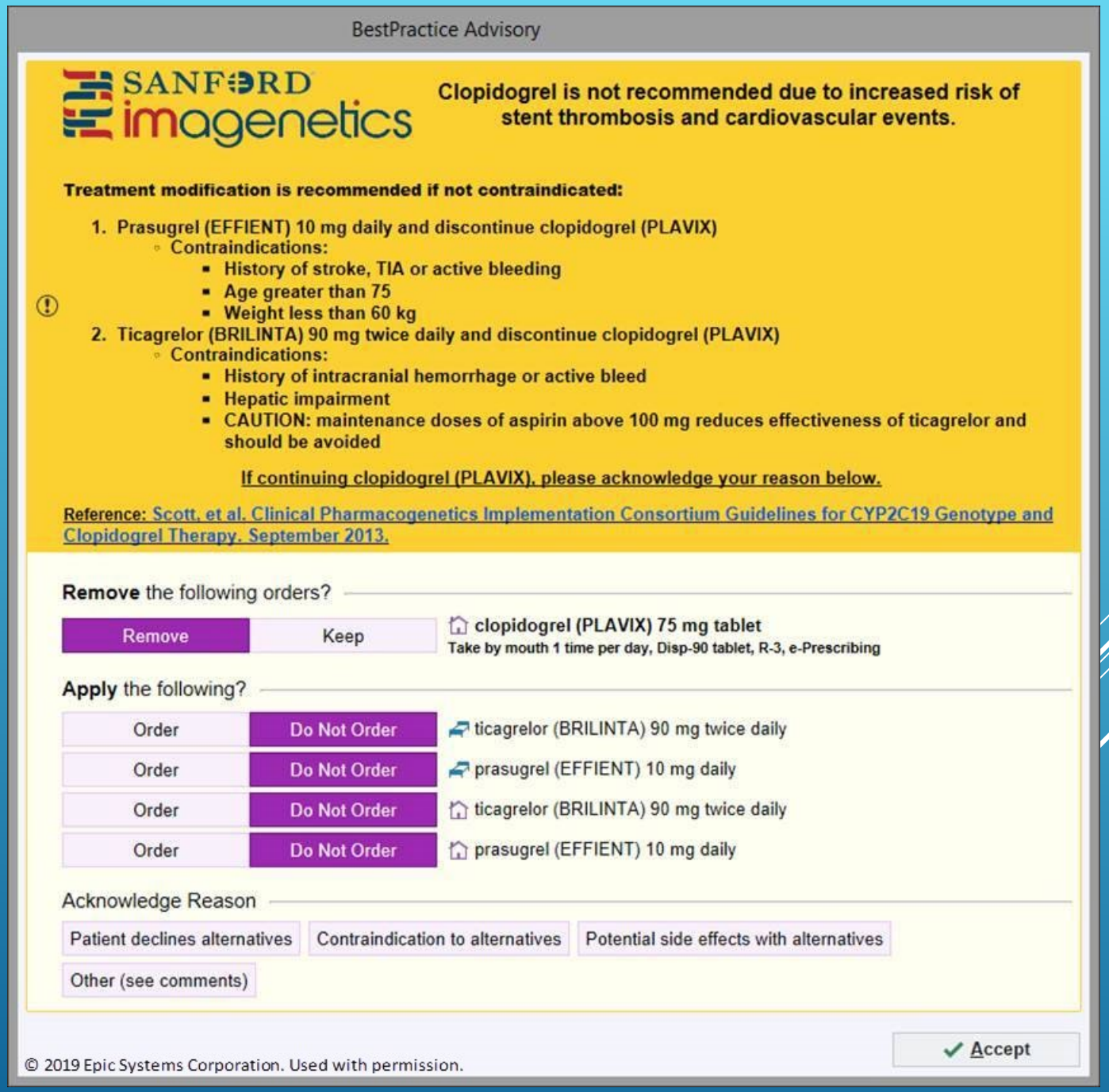
If you see Extensive Metabolizer, that essentially means Normal Metabolizer

The distribution of common variant alleles of CYP genes varies among different ethnic populations.

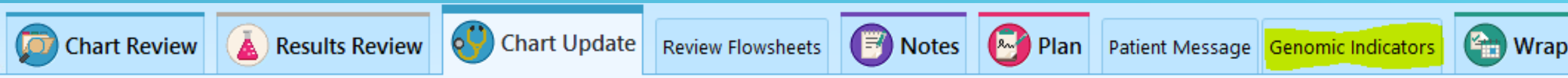
Example: CYP2C19: 2-4% African Americans, 3-5% Caucasians, 15-20% Asians are poor metabolizers

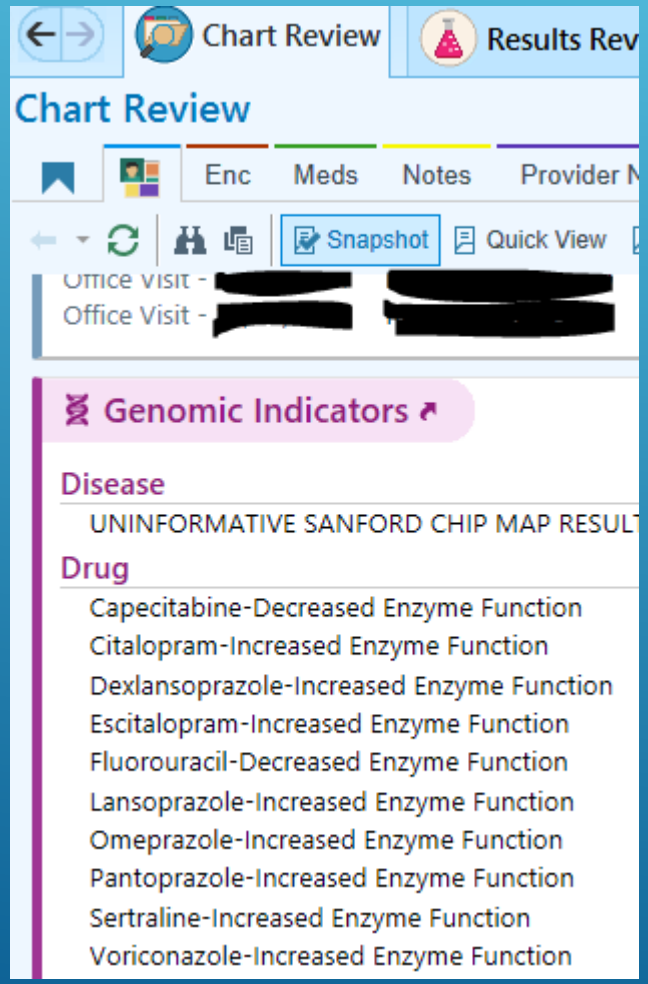
ALERTS WITHIN ELECTRONIC MEDICAL RECORD

- Lab results/reports available in EMR
- Best Practice Alerts (BPA's) built and programmed to fire for providers as appropriate



GENOMIC INDICATORS





Hover over for more information

CYP2C19 EXAMPLE

- Pharmacogenomic testing may help determine what medications and what doses will be the most effective and beneficial for your patients based on the phenotype/genotype of alleles

- For example, if patient is a CYP2C19 poor metabolizer clopidogrel will not be adequate for antiplatelet therapy and a different medication should be used
  - Approximately 1 out of 5 patients have at least one abnormal copy of the CYP2C19 gene and as many as 1 in 20 patients have two abnormal copies of the CYP2C19 gene
  - Patients who have a reduced ability to effectively metabolize clopidogrel are **three times more likely to develop a clot on a stent**
  - Poor metabolizers (loss of CYP2C19 activity) have **2X the risk** of having a subsequent adverse cardiac event while receiving treatment with clopidogrel after a myocardial infarction

CYP2C19

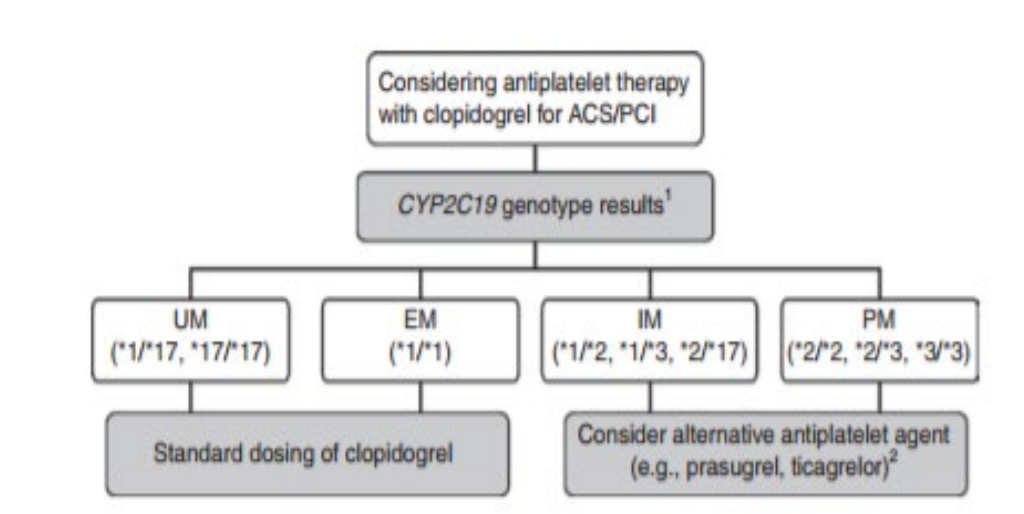
- CYP2C19 = liver enzyme, polymorphic, responsible for metabolism for several medications (Plavix, SSRI's, TCA's, etc)
- CYP2C19 is responsible for the conversion of clopidogrel (prodrug) to its active metabolite
- Normal function = *1
- Non function alleles = *2 rs4244285, *3-*8
- Increased activity = *17
- 1 or 2 non-function alleles results in decreased or no platelet inhibition

PATIENT CASE #1

- 73 yo female
- Arrives via ambulance with sudden onset of shortness of breath, nausea, and pain in the jaw
- Troponin elevated – ST segment deviation on EKG
- Cath lab for percutaneous coronary intervention – stents placed
- Patient requires antiplatelet therapy to decrease stent thrombosis - clopidogrel

PATIENT CASE #1

- MD orders clopidogrel 75 mg by mouth daily and a CYP2C19 test
- 2 days later -> Pgx result *2/*3 = poor metabolizer
- Call made to patient – change to ticagrelor 90 mg by mouth twice a day



CYP2D6 AND CYP2C19

- CYP2D6 = liver enzyme, polymorphic, responsible for metabolism for several medications (SSRI's, TCA's, codeine, tramadol, etc.)
- CYP2D6 and CYP2C19 responsible for metabolism of SSRI's and TCA's
- Copy number = "xN" (duplication/multiplication)
- Drug-gene variants can cause therapeutic failure or increase in adverse effects

PATIENT CASE #2

- 12 yo female hx of major depression, anxiety, insomnia, decreased appetite, abdominal pain, and suicidal ideation – 2 admissions to behavioral health institution
- Counselor biweekly, stops eating (lost 5 pounds) and sleeping, missing school, cries continuously and states "I don't want to do this anymore"
- Increased feelings of helplessness and guilt, parent-child relationship issues
- Texted a friend stating that she was hoping she would have died overnight

- fluoxetine 20 mg>fluoxetine 30 mg>bupropion XL>Topiramate
  - Fluoxetine and Topiramate d/c'd due to side effects
  - Bupropion XL – not seeing much benefit

PATIENT CASE #2

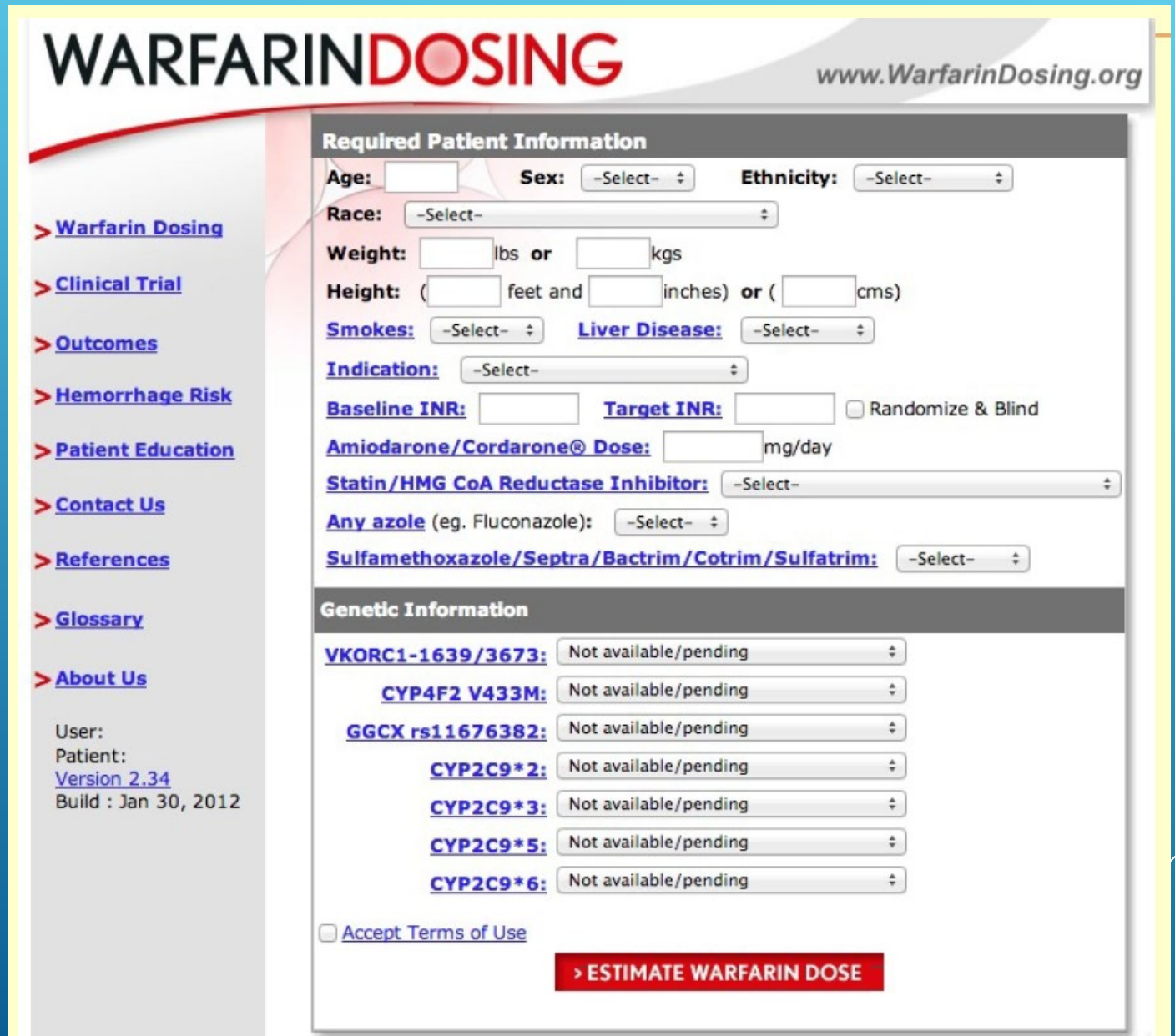
- Basic pharmacogenomics panel
  - CYP2D6: *4/*4 = poor metabolizer
  - CYP2C19: *1/*1 – normal metabolizer
- Per CPIC guidelines: avoid TCA's, fluvoxamine and paroxetine.
- Avoid fluoxetine due to previous side effects (metabolized by CYP2D6
- Consider escitalopram, citalopram or sertraline–> escitalopram 10 mg po daily started
- 4 week update: significant improvement in depression, anxiety improved slightly, no thoughts of suicide, increased interest in activities, work caught up in school, sleeping better, abdominal pain resolved
- 8 week update: mood completely stabilized

PATIENT CASE #2 – ADDITIONAL INFO

- Pediatric patients caveats
  - Very few guidelines/studies
    - Chemo agents
    - Chemo rescue
    - Supportive meds
  - Reactive testing instead of preemptive
  - Enzyme maturation – extrapolate results depending on gene

WARFARIN

WARFARIN DOSING RESOURCE



METABOLISM IMPLICATIONS

Citalopam (Active drug)

- Ultra-rapid Metabolizer
  - Increased metabolism when compared to normal metabolizers.
  - Lower plasma concentrations will increase probability of pharmacotherapy failure.
- Poor Metabolizer
  - Greatly reduced metabolism when compared to normal metabolizers.
  - Higher plasma concentrations may increase the probability of side effects.

Codeine (Pro-drug)

- Ultra-rapid Metabolizer
  - Increased formation of morphine following codeine administration
  - higher risk of toxicity
- Poor Metabolizer
  - Greatly reduced morphine formation following codeine administration
  - Can lead to insufficient pain relief

METABOLISM IMPLICATIONS

Clopidogrel (ProDrug)

- UM
  - Increased platelet inhibition
  - Decreased residual platelet aggregation
- PM
  - Significantly reduced platelet inhibition;
  - Increased residual platelet aggregation
  - **Increased risk for adverse cardiovascular events**
    - **Due to lack of efficacy**

Sertraline (active drug)

- UM
  - Increased metabolism when compared to extensive metabolizers.
- PM
  - Greatly reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may **increase the probability of side effects.**

TO NOTE

- A particular genetic variant may increase the likelihood of an adverse reaction but it will not guarantee it
  - some people with the variant may not experience an adverse reaction to a drug
- Remember, if an individual doesn't have the gene variant it doesn't mean they won't experience an adverse reaction

CONCLUSION

- Pgx has utility in some areas, but not all
- Know and navigate your resources
- Understand the evidence
- PGx results are just another piece of the puzzle

THANK-YOU!

QUESTIONS?