UNC
CENTER FOR
PHARMACOGENOMICS AND
INDIVIDUALIZED THERAPY

Will you please give me the right drug!

Tim Wiltshire, PhD
Director, Center for Pharmacogenomics and Individualized Therapy
Associate Professor, UNC Eshelman School of Pharmacy

May 25th, 2017

Have you had precision therapy?

What Conditions are Screened For in North Carolina?

Amino Acid Disorders
- Argininosuccinic Aciduria (ASA)
- Benign Hyperphenylalaninemia (H-PHE)
- Citrullinemia, Type I (CIT)
- **Classic Phenylketonuria (PKU)**
- Homocystinuria (HCY)
- Maple Syrup Urine Disease (MSUD)
- Tyrosinemia, Type II (TYR II)
- Tyrosinemia, Type III (TYR III)

Endocrine Disorders
- Congenital Adrenal Hyperplasia (CAH)
- Primary Congenital Hypothyroidism (CH)

Fatty Acid Oxidation Disorders
- Carnitine Acylcarnitine Translocase Deficiency (CACT)
- Carnitine Palmitoyltransferase Type II Deficiency (CPT-II)
- Glutaric Acidemia, Type II (GA-2)
- Long-Chain L-3 Hydroxyacyl-CoA Dehydrogenase Deficiency
- Medium-Chain Acyl-CoA Dehydrogenase Deficiency (MCAD)
- Short-Chain Acyl-CoA Dehydrogenase Deficiency (SCAD)
- Trifunctional Protein Deficiency (TFP)
- Very Long-Chain Acyl-CoA Dehydrogenase Deficiency (VLCAD)

37 conditions

Hemoglobin Disorders
- Hemoglobinopathies (Var Hb)
- S, Beta-Thalassemia (Hb S/βTh)
- S, C Disease (Hb S/C)
- Sickle Cell Anemia (Hb SS)

Organic Acid Disorders
- 2-Methylbutyrylglycinuria (2MBG)
- 3-Hydroxy-3-Methylglutaric Aciduria (HMG)
- 3-Methylcrotonyl-CoA Carboxylase Deficiency (3-MCC)
- Beta-Ketothiolase Deficiency (BKT)
- Glutaric Acidemia, Type I (GA-1)
- Holocarboxylase Synthetase Deficiency (MCD)
- Isobutyrylglycinuria (IBG)
- Isovaleric Acidemia (IVA)
- Methylmalonic Acidemia (Cobalamin Disorders) (cblA,B)
- Methylmalonic Acidemia (Methymalonyl-CoA Mutase Deficiency)
- Propionic Acidemia (PROP)

Other Disorders
- Biotinidase Deficiency (BIOT)
- Classic Galactosemia (GALT)
- Critical Congenital Heart Disease (CCHD)
  State preferred name: Critical congenital heart defect
- Cystic Fibrosis (CF)
- Hearing loss (HEAR)

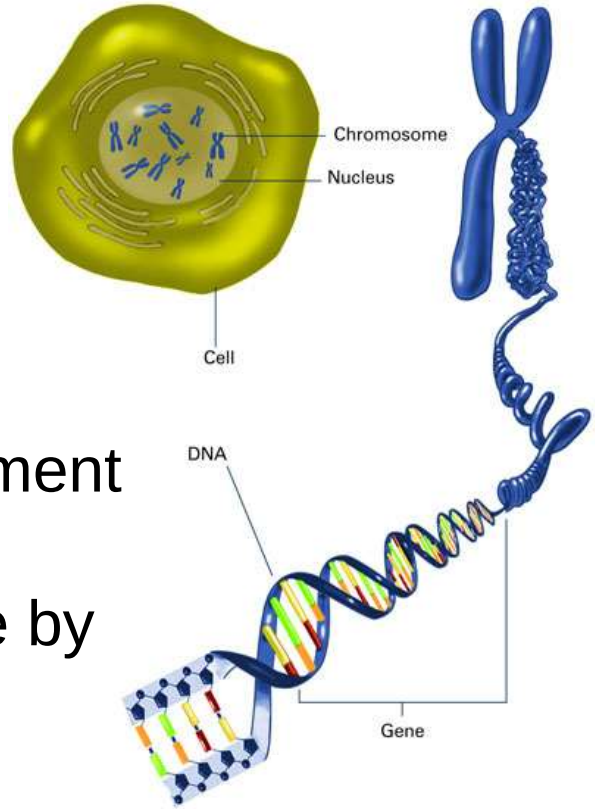
Phenylketonuria (commonly known as PKU) is an inherited disorder that increases the levels of a substance called phenylalanine in the blood. Phenylalanine is a building block of proteins (an amino acid) that is obtained through the diet. It is found in all proteins and in some artificial sweeteners. If PKU is not treated, phenylalanine can build up to harmful levels in the body, causing intellectual disability and other serious health problems.

The signs and symptoms of PKU vary from mild to severe. The most severe form of this disorder is known as classic PKU. Infants with classic PKU appear normal until they are a few months old. Without treatment, these children develop permanent intellectual disability. Seizures, delayed development, behavioral problems, and psychiatric disorders are also common.

http://www.ncdhhs.gov/dph/wch/families/newbornmetabolic.htm

Variation in the Human Genome

- Our genome contains 3 billion base pairs of DNA
- Between 2 people, there are approximately 3 million base pair differences
- Understanding variation has shown promise for improving disease treatment and outcomes
- Variation can change drug response by affecting pharmacokinetics or pharmacodynamics



National Institute of General Medical Sciences

Variation in the Human Genome

- Single nucleotide polymorphism (SNP)
  - Most common cause of genetic variation
  - Example: *VKORC1* 1173 C>T
- Other polymorphisms:
  - Insertions
  - Deletions
  - Duplications

Treatment reason

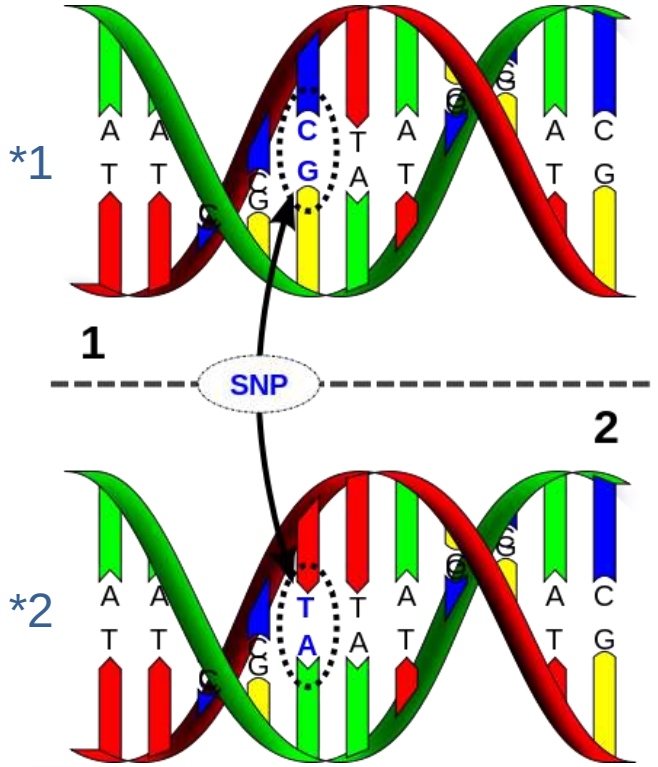
Unable to eat, diarrhea

Unable to eat diarrhea

Polymorphism

"Poly" *Many*

"Morphe" *Form*



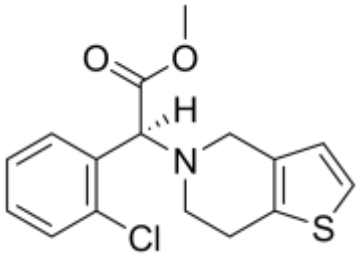
Variation in the Human Genome

- Different versions of a gene are called alleles
  - Example: *CYP2C19* *1/*2

Allele	Function	Frequency of CYP2C19 Variants (%)	
		Caucasian/African American	Asian
1	**Wild-Type**	**-**	**-**
2	**Loss**	**10-15**	**30-35**
3	**Loss**	**<1**	**5-10**
17	**Gain**	**16-22**	**1-3**

Predicting Efficacy

- Approximately 25% of patients on clopidogrel experience a sub-therapeutic response

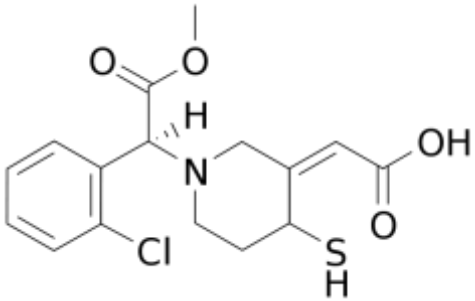


Clopidogrel (Prodrug)

Cytochrome P450
1A2
2B6
X **2C19**

Intermediate Metabolite

Decrease



Cytochrome P450
3A4
3A5
2B6
2C9
X **2C19**

Active Metabolite

Decrease

Therapeutic Failure

Black Box Warning

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

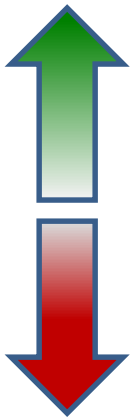
See full prescribing information for complete boxed warning.

- **Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1)**
- **Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. (12.5)**
- **Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5)**
- **Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)**

Plavix® prescribing information: 3/12/2010

CYP2C19 Polymorphisms

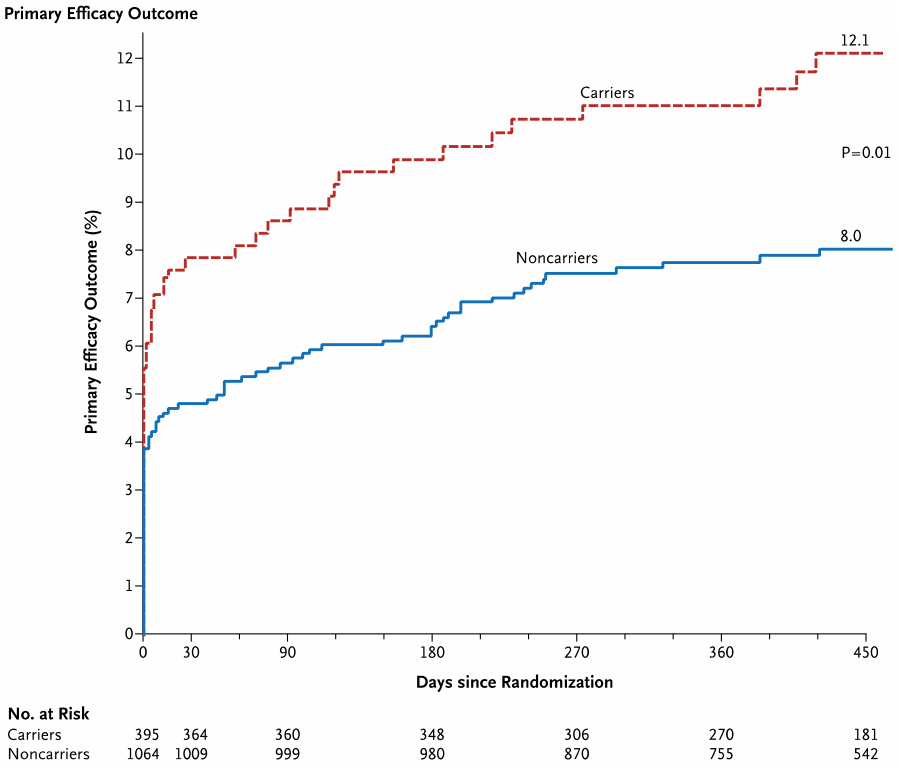
- Genetic variation in *CYP2C19* is common and is influenced by race/ethnicity
  - ***1* = wild-type allele** *(minor allele frequencies)*
  - ***2* = loss-of-function allele** (Caucasians/AA: 10-15% Asians: 30-35%)
  - ***3* = loss-of-function allele** (Caucasians/AA: <1% Asians: 5-10%)
  - ***17* = gain-of-function allele**(Caucasians/AA: 16-22% Asians: 1-3%)

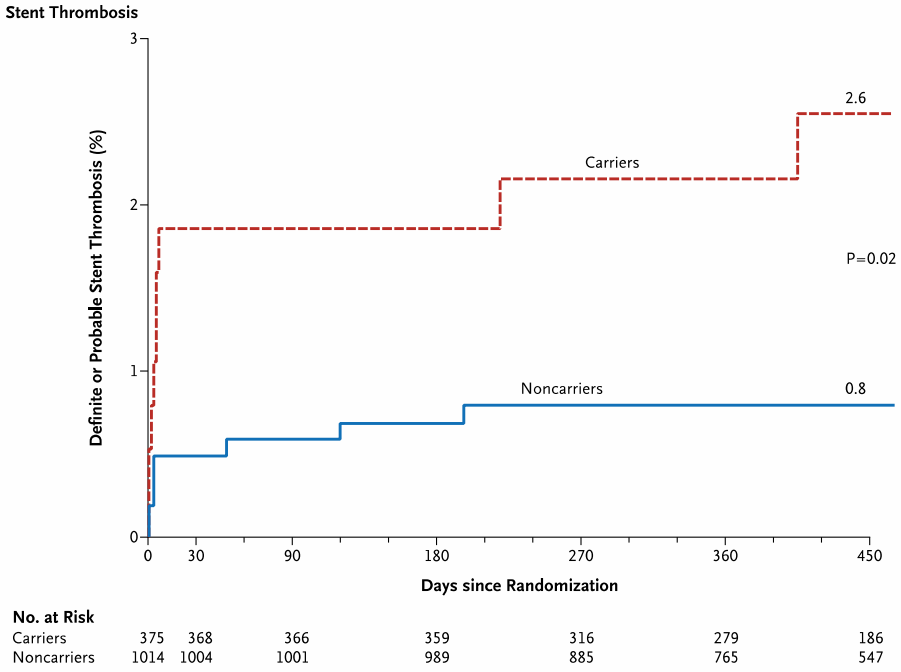


Metabolizer Phenotype	Genotype	U.S. (%)
Ultra-rapid	***17/*17**	1-5%
Rapid	***1/*17**	20-30%
Extensive	***1/*1**	35-50%
Intermediate	***1/*2** or ***1/*3** or ***2/*17** or ***3/*17**	20-30%
Poor	***2/*2** or ***2/*3** or ***3/*3**	1-5%

CYP2C19 Status and Outcomes in Subjects Receiving Clopidogrel

(Composite of Death due to Cardiovascular Causes, Myocardial Infarction, and Stroke)





Carriers = Reduced Function Allele (*2 or *3)

Mega JL, et al. N Engl J Med 2009;360:354-362.

UNC algorithm

"High risk" patient undergoing PCI

P2Y12 inhibitor initiation
(clinician discretion)

CYP2C19 genotype obtained
(in medical record within 24-48 hours)

Follow-up on *CYP2C19* genotyping result
(continue or switch P2Y12 inhibitor ?)

65-70%	*3-5%*	*25-30%*
EM (**1/*1, *1/*17*)	UEM (**17/*17*)	IM / PM (any **2* or **3* carrier)
Clopidogrel	Clopid, Pras or Ticag *(clinician discretion)*	Prasugrel or Ticagrelor *(clinician discretion)*

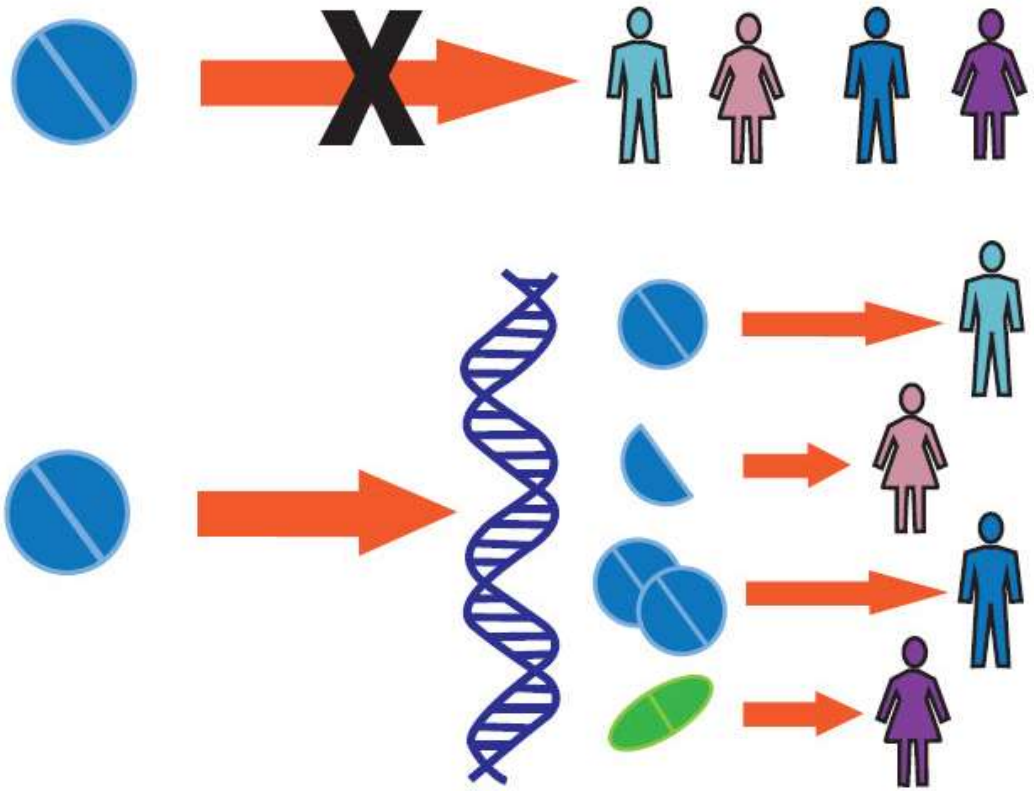
Current Model: Imprecision Medicine

Blue = Treatment Success

Red = Treatment Failure

Schork NJ. *Nature* 2015;520:609-611.

Utilizing Genotype Data



Predict efficacy

Optimize dose

Prevent ADRs

http://medicine.iupui.edu/IIPM

Limitations in Clinical Practice

- Medical record implementation
- Health system logistics
- **Turnaround time**
- **Cost and insurance coverage**
- Privacy and trust
- Clinician education
- **Clear medical recommendations**

Your Pharmacogenomic Report Card

R scanner

i-nigma QR Reader

Your pharmacogenetic profile

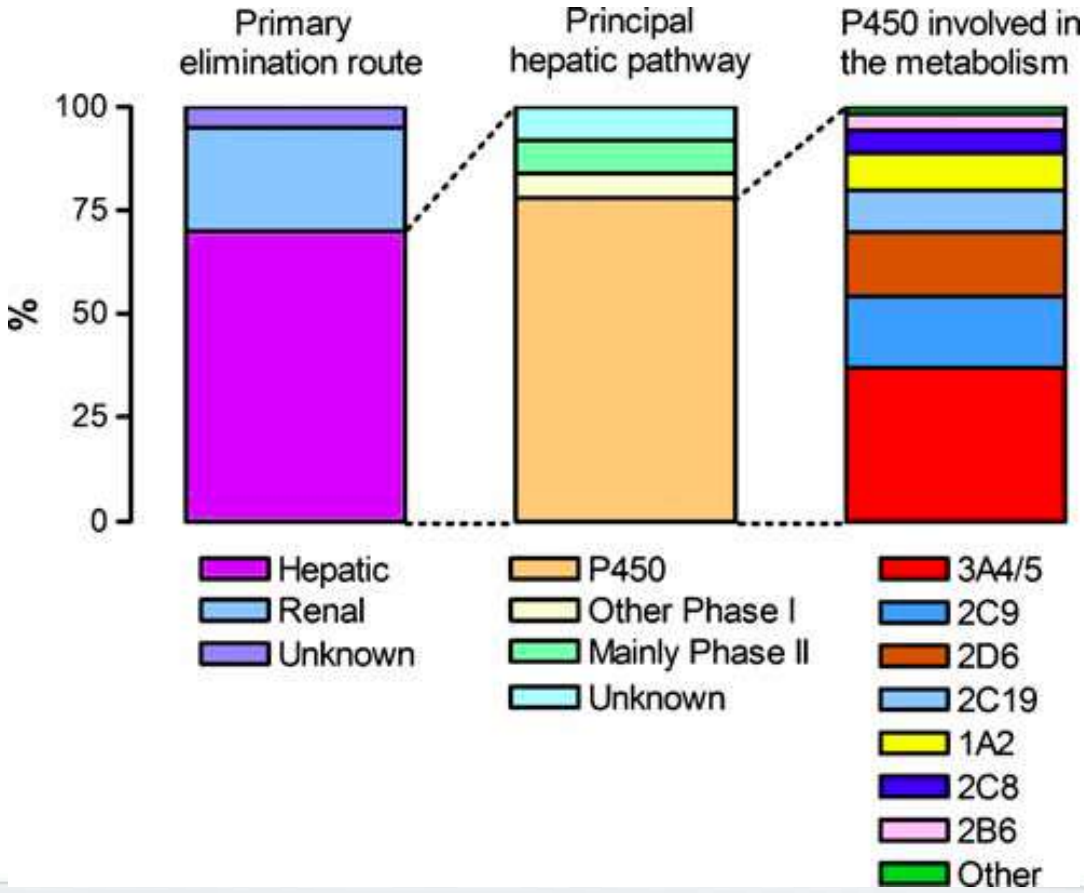
Gene	Genotype-Haplotype	Phenotype
CYP2B6	*1/*9	Extensive metabolizer
CYP2C9	*1/*1	Extensive metabolizer
CYP2C19	*2A/*35	Poor metabolizer
CYP2D6	*1/*41	Intermediate metabolizer
CYP3A4	*1/*1	Extensive metabolizer
CYP3A5	*3A/*3A	Poor metabolizer
CYP4F2	*1/*3	Intermediate metabolizer
VKORC1	H1/H2	Intermediate sensitivity to Warfarin
SLCO1B1	*1A/*14 or *1B/*4	Extensive function
ABCB1	*2/*2	Low function
NAT2	*5B/*5B	Poor acetylator
TPMT	*1/*1	Extensive metabolizer
BCHE	*1/*1	Extensive function
UGT1A1	*37/*80	Poor metabolizer
DPYD	*1/*1	Extensive metabolizer
NUDT15	*1/*1	Thiopurines resistance
G6PD	B	

Routes of elimination for the top 200 drugs by prescription

- Most drugs are metabolized by enzymes from the cytochrome (CYP) P450 family.
- Of 57 known CYP families, four are responsible for processing about 90% of drugs

Within this gene family molecular variation at loci coding for CYP2C9, CYP2C19, and CYP2D6 have the most important clinical consequences.

CYP2D6 is one of the best characterized. It is highly polymorphic with more than 60 major genetic variants.



CYP2C19 Variation

Allele	Allele Functional Status	African Allele Frequency	African American Allele Frequency	Caucasian (European + North American) Allele Frequency	Americas Allele Frequency	Diplotype	Coded Genotype/Phenotype Summary	Diplotype	Coded Genotype/Phenotype Summary
*1	Normal function	0.331	0.570	0.621	0.670	*1/*1	none		
*2	No function	0.142	0.183	0.146	0.131	*1/*2	Intermediate Metabolizer	*2/*2	Poor Metabolizer
*3	No function	0.008	0.003	0.006	0.003	*1/*3	Intermediate Metabolizer	*2/*3	Poor Metabolizer
*4A	No function	0.000	0.000	0.003	0.000	*1/*4A	Intermediate Metabolizer	*2/*4A	Poor Metabolizer
*4B	No function		0.000			*1/*4B	Intermediate Metabolizer	*2/*4B	Poor Metabolizer
*5	No function	0.000	0.000	0.000	0.000	*1/*5	Intermediate Metabolizer	*2/*5	Poor Metabolizer
*6	No function	0.000	0.000	0.001	0.000	*1/*6	Intermediate Metabolizer	*2/*6	Poor Metabolizer
*7	No function	0.000	0.000	0.000	0.000	*1/*7	Intermediate Metabolizer	*2/*7	Poor Metabolizer
*8	No function	0.000	0.002	0.003	0.001	*1/*8	Intermediate Metabolizer	*2/*8	Poor Metabolizer
*9	Decreased function	0.042	0.011	0.000	0.001	*1/*9	Likely Intermediate Metabolizer	*2/*9	Likely Poor Metabolizer
*10	Decreased function	0.000	0.004	0.000	0.001	*1/*10	Likely Intermediate Metabolizer	*2/*10	Likely Poor Metabolizer
*11	Normal function					*1/*11	none	*2/*11	Intermediate Metabolizer
*12	Unknown function	0.000	0.002	0.000	0.000	*1/*12	Indeterminate	*2/*12	Indeterminate
*13	Normal function	0.000	0.012	0.001	0.004	*1/*13	none	*2/*13	Intermediate Metabolizer
*14	Unknown function	0.000	0.000	0.000	0.000	*1/*14	Indeterminate	*2/*14	Indeterminate
*15	Normal function	0.057	0.014	0.002	0.004	*1/*15	none	*2/*15	Intermediate Metabolizer
*16	Decreased function		0.000	0.000	0.000	*1/*16	Likely Intermediate Metabolizer	*2/*16	Likely Poor Metabolizer
*17	Increased function	0.151	0.201	0.213	0.163	*1/*17	Rapid Metabolizer	*2/*17	Intermediate Metabolizer
*18	Normal function					*1/*18	none	*2/*18	Intermediate Metabolizer
*19	Decreased function					*1/*19	Likely Intermediate Metabolizer	*2/*19	Likely Poor Metabolizer
*22	No function		0.000	0.000	0.000	*1/*22	Intermediate Metabolizer	*2/*22	Poor Metabolizer
*23	Unknown function					*1/*23	Indeterminate	*2/*23	Indeterminate
*24	No function					*1/*24	Intermediate Metabolizer	*2/*24	Poor Metabolizer
*25	Decreased function					*1/*25	Likely Intermediate Metabolizer	*2/*25	Likely Poor Metabolizer
*26	Decreased function					*1/*26	Likely Intermediate Metabolizer	*2/*26	Likely Poor Metabolizer
*27	Unknown function	0.218				*1/*27	Indeterminate	*2/*27	Indeterminate
*28	Normal function	0.007				*1/*28	none	*2/*28	Intermediate Metabolizer
*29	Unknown function					*1/*29	Indeterminate	*2/*29	Indeterminate
*30	Unknown function					*1/*30	Indeterminate	*2/*30	Indeterminate
*31	Unknown function					*1/*31	Indeterminate	*2/*31	Indeterminate
*32	Unknown function					*1/*32	Indeterminate	*2/*32	Indeterminate
*33	Unknown function					*1/*33	Indeterminate	*2/*33	Indeterminate
*34	Unknown function					*1/*34	Indeterminate	*2/*34	Indeterminate
*35	No function	0.031	0.008	0.000	0.021	*1/*35	Intermediate Metabolizer	*2/*35	Poor Metabolizer

Genotype/Haplotype Details

CYP2C19

Allele Tested: *1A, *1B, *2A, *3, *4, *5A, *5B, *6, *7, *8, *9, *10, *16, *17, *19, *22, *24, *25, *26, *27, *35.

Genetic results: CYP2C19 *1B/*1B

Phenotype: Extensive metabolizer

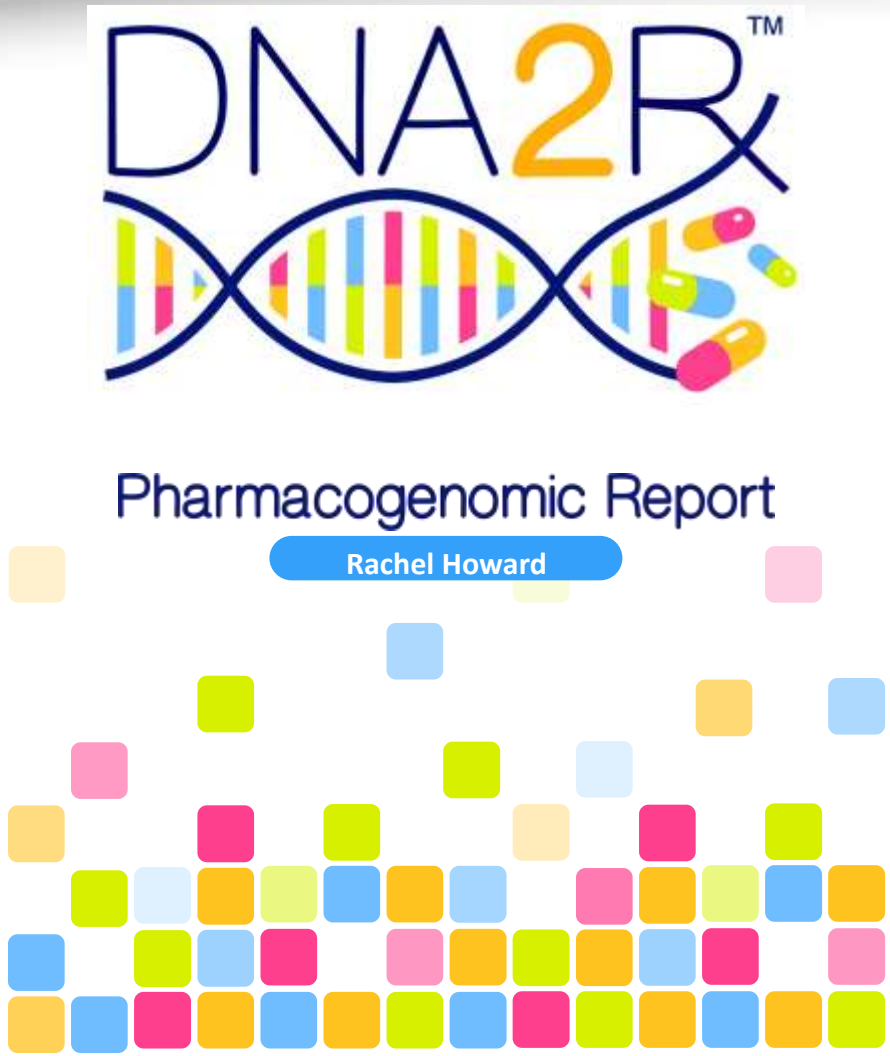
Gene	Protein change	Nucleotide change	Allele	Marker	Genotype
CYP2C19	Ile331Val	991A>G	*1B	rs3758581	G/G
CYP2C19	Splicing defect	681G>A	*2	rs4244285	G/G
CYP2C19	Trp212Ter	636G>A	*3	rs4986893	G/G
CYP2C19	Met1Val	1A>G	*4	rs28399504	A/A
CYP2C19	Arg433Trp	1297C>T	*5	rs56337013	C/C
CYP2C19	Arg132Gln	395G>A	*6	rs72552267	G/G
CYP2C19	Splicing defect	819+2T>A	*7	rs72558186	T/T
CYP2C19	Trp120Arg	358T>C	*8	rs41291556	T/T
CYP2C19	Arg144His	431G>A	*9	rs17884712	G/G
CYP2C19	Pro227Leu	680C>T	*10	rs6413438	C/C
CYP2C19	Arg442Cys	1324C>T	*16	rs192154563	C/C
CYP2C19		-806C>T	*17	rs12248560	C/C
CYP2C19	Ser51Gly	151A>G	*19	151A>G-Ser51Gly	A/A
CYP2C19	Arg186Pro	557G>C	*22	rs140278421	G/G
CYP2C19	Arg335Gln	1004G>A	*24	rs118203757	G/G
CYP2C19	Phe448Leu	1344C>G	*25	rs118203759	C/C
CYP2C19	Asp256Asn	766G>A	*26	766G>A-Asp256Asn	G/G
CYP2C19		-1041G>A	*27	rs7902257	G/G
CYP2C19		332-23A>G	*35	rs12769205	A/A

CYP2C19 is the most important gene in the metabolism of: Brivaracetam, Carisoprodol, Citalopram, Clobazam, Clopidogrel, Dexlansoprazole, Diazepam, Enfuvirtide Esomeprazole, Flunitrazepam, Hexobarbital, Mephenytoin, Moclobemide, Nelfinavir, Nilutamide, Omeprazole, Pantoprazole, Pentamidine, Phenobarbital, Phenytoin, Proguanil Rabeprazole, Temazepam, Teniposide, Voriconazole.

Drugs and substances known to induce CYP2C19 activity include: Artemisinin, Carbamazepine, Efavirenz, Norethisterone, Rifampicin, Ritonavir, St. John's Wort.

Drugs and substances known to inhibit CYP2C19 activity include: Chloramphenicol, Esomeprazole, Felbamate, Fluvoxamine, Isoniazid, Lansoprazole, Moclobemide, Omeprazole.

Your Pharmacogenomic Report



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Gene	Genotype-Haplotype	Phenotype
CYP2B6	*1/*1	Extensive metabolizer
CYP2C9	*1/*1	Extensive metabolizer
CYP2C19	*1B/*1B	Extensive metabolizer
CYP2D6	*1/*1	Extensive metabolizer
CYP3A4	*1/*1	Extensive metabolizer
CYP3A5	*1A/*1A	Extensive metabolizer
CYP4F2	*1/*1	Extensive metabolizer
VKORC1	H1/H7	Warfarin resistance
SLCO1B1	*1A/*1A	Extensive function
ABCB1	*1/*1	Extensive function
NAT2	*4/*4	Ultrarapid acetylator
TPMT	*1/*1	Extensive metabolizer
BCHE	*1/*1	Extensive function
UGT1A1	*1/*1	Extensive metabolizer
DPYD	*1/*1	Extensive metabolizer
NUDT15	*1/*1	Thiopurines resistance
RYR1	*1/*1	
G6PD	B/B	

PGx Report - Pain Management

Type: Opioid

Drug Class	Generic	Primary Mechanism Involved	Other Mechanisms Involved	May Have Decreased Efficacy	Used As Directed	May Have Increased Toxicity
Opioid Analgesics						
Opium alkaloids	Codeine	CYP2D6	CYP3A4, CYP3A5		●	
Ethers of morphine	Dihydrocodeine	CYP3A4	CYP2D6, CYP3A5			●
	Ethylmorphine	CYP2D6	CYP3A4, CYP3A5			●
Semi-synthetic alkaloid derivatives	Hydrocodone	CYP2D6	CYP3A4, CYP3A5, OPRM1			●
	Oxycodone	CYP3A4	CYP3A5, CYP2D6, ABCB1, UGT2B7, COMT		●	
Synthetic opioids						
Anilidopiperidine derivatives	Alfentanyl	CYP3A4	CYP3A5, ABCB1, OPRM1		●	
	Fentanyl	CYP3A4	CYP3A5, ABCB1, OPRM1		●	
	Sufentanil	CYP3A4	CYP3A5, OPRM1		●	
Phenylpiperidine derivatives	Meperidine	CYP2B6	CYP3A4, CYP2C19, CYP3A5, UGT1A4			●
	Ketobemidone	CYP2C9	CYP3A4, CYP3A5		●	
Diphenylpropylamine derivatives	Dextropropoxyphene	CYP3A4	CYP3A5, Renal Excretion			●
	Levacetylmethadol	CYP3A4	CYP3A5		●	
	Loperamide	CYP3A4	CYP3A5		●	
	Methadone	CYP3A4	CYP2B6, CYP2D6, CYP3A5, ABCB1, UGT2B7, COMT		●	
Oripavine derivatives	Buprenorphine	CYP3A4	CYP3A5, UGT1A1			●
Morphinan derivatives	Dextromethorphan	CYP2D6	CYP3A4, CYP3A5			●
Others	Tramadol	CYP2D6	CYP3A4, CYP2B6, CYP3A5, OPRM1, SLC22A1, COMT		●	
	Tapentadol	CYP2C9	CYP2C19, CYP2D6			●
	Tilidine	CYP3A4	CYP2C19, CYP3A5			●
Anti-opioid	Methylnaltrexone	CYP2D6	CYP3A4, CYP3A5			

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Search for

CYP2D6 plavix

view legend

Limit results to: Genes Variants Chemicals Diseases Pathways Publications Dosing Guidelines Drug Labels Clinical Annotations

Results 1 - 20 of top 500, sorted by relevance

VA	Disease: dose reduction [pgx research]
VA	Disease: time to achieve stable dose [pgx research]
DG	DosingGuideline: Annotation of CPIC Guideline for amitriptyline and CYP2C19,CYP2D6
DG	DosingGuideline: Annotation of CPIC Guideline for imipramine and CYP2C19,CYP2D6
DG	DosingGuideline: Annotation of CPIC Guideline for doxepin and CYP2C19,CYP2D6
DG	DosingGuideline: Annotation of CPIC Guideline for trimipramine and CYP2C19,CYP2D6
DG	DosingGuideline: Annotation of CPIC Guideline for clomipramine and CYP2C19,CYP2D6
DG	DosingGuideline: Annotation of CPIC Guideline for warfarin and CYP2C9,CYP4F2,VKORC1
DG	DosingGuideline: Annotation of CPIC Guideline for desipramine and CYP2D6
DG	DosingGuideline: Annotation of CPIC Guideline for nortriptyline and CYP2D6
DG	DosingGuideline: Annotation of CPIC Guideline for azathioprine and TPMT
DG	DosingGuideline: Annotation of CPIC Guideline for mercaptopurine and TPMT
DG	DosingGuideline: Annotation of CPIC Guideline for simvastatin and SLCO1B1

from search: plavix

CHEMICAL: PRODRUG

clopidogrel

Clinical PGx | PGx Research | Overview | Properties | Pathways | Is Related To | Publications | LinkOuts

Prescribing Info (5) | **Drug Labels (4)** | **Clinical Annotations (42)**

Available Prescribing Info

Dosing Guidelines

1. Annotation of CPIC Guideline for clopidogrel and CYP2C19
2. Annotation of DPWG Guideline for clopidogrel and CYP2C19

Rx Annotations

1. A pharmacodynamic comparison of a personalized strategy for anti-platelet therapy versus ticagrelor in achieving a therapeutic window
2. Optimizing clopidogrel dose response: a new clinical algorithm comprising CYP2C19 pharmacogenetics and drug interactions
3. Switching from prasugrel to clopidogrel based on Cytochrome P450 2C19 genotyping in East Asian patients stabilized after acute myocardial infarction

1. Annotation of CPIC Guideline for clopidogrel and CYP2C19

last updated 03/15/2017

Summary

The CPIC Dosing Guideline for clopidogrel recommends an alternative antiplatelet therapy (e.g., prasugrel, ticagrelor) for CYP2C19 poor or intermediate metabolizers if there is no contraindication.

Specify a genotype for specific annotations

Help with allele options

Alleles not present in the pull-down menus have no CPIC recommendation.

Pick alleles for **CYP2C19**: -- --

CHEMICAL: PRODRUG
clopidogrel

Clinical PGx | PGx Research | Overview | Properties | Pathways | Is Related To | Publications | LinkOuts

Prescribing Info (5) | **Drug Labels (4)** | **Clinical Annotations (42)**

Available Prescribing Info

Dosing Guidelines
1. Annotation of CPIC Guideline for clopidogrel and CYP2C19
2. Annotation of DPWG Guideline for clopidogrel and CYP2C19

Rx Annotations
1. A pharmacodynamic comparison of a personalized strategy for anti-platelet therapy versus ticagrelor in achieving a therapeutic window
2. Optimizing clopidogrel dose response: a new clinical algorithm comprising CYP2C19 pharmacogenetics and drug interactions
3. Switching from prasugrel to clopidogrel based on Cytochrome P450 2C19 genotyping in East Asian patients stabilized after acute myocardial infarction

1. Annotation of CPIC Guideline ... **ogrel and CYP2C19**

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Summary

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Specify a genotype for specific an...

Help with allele options

Alleles not present in the pull-down menus ha... commendation.

Pick alleles for **CYP2C19**: *1 --

-- *1 *2 *3 *4A *4B *5 *6 *7 *8 *17

Annotation

Dosing guidelines for clopidogrel with *1/*3 alleles of CYP2C19

Pick alleles for **CYP2C19**: *1 *3

Implications	Reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events
Metabolizer Status	Intermediate Metabolizer
Phenotype (Genotype)	An individual carrying one normal function allele and one no function allele or one increased function allele and no function allele. *The predicted metabolizer phenotype for *2-*8/*17 genotypes are provisional classifications. The currently available evidence indicates that the *17 increased function allele is unable to completely compensate for the *2 no function allele [Article:20492469]; however, this data has not been consistently replicated and is therefore a provisional classification.*
Recommendations	Alternative antiplatelet therapy (if no contraindication); e.g., prasugrel, ticagrelor
Classification of Recommendation	Moderate

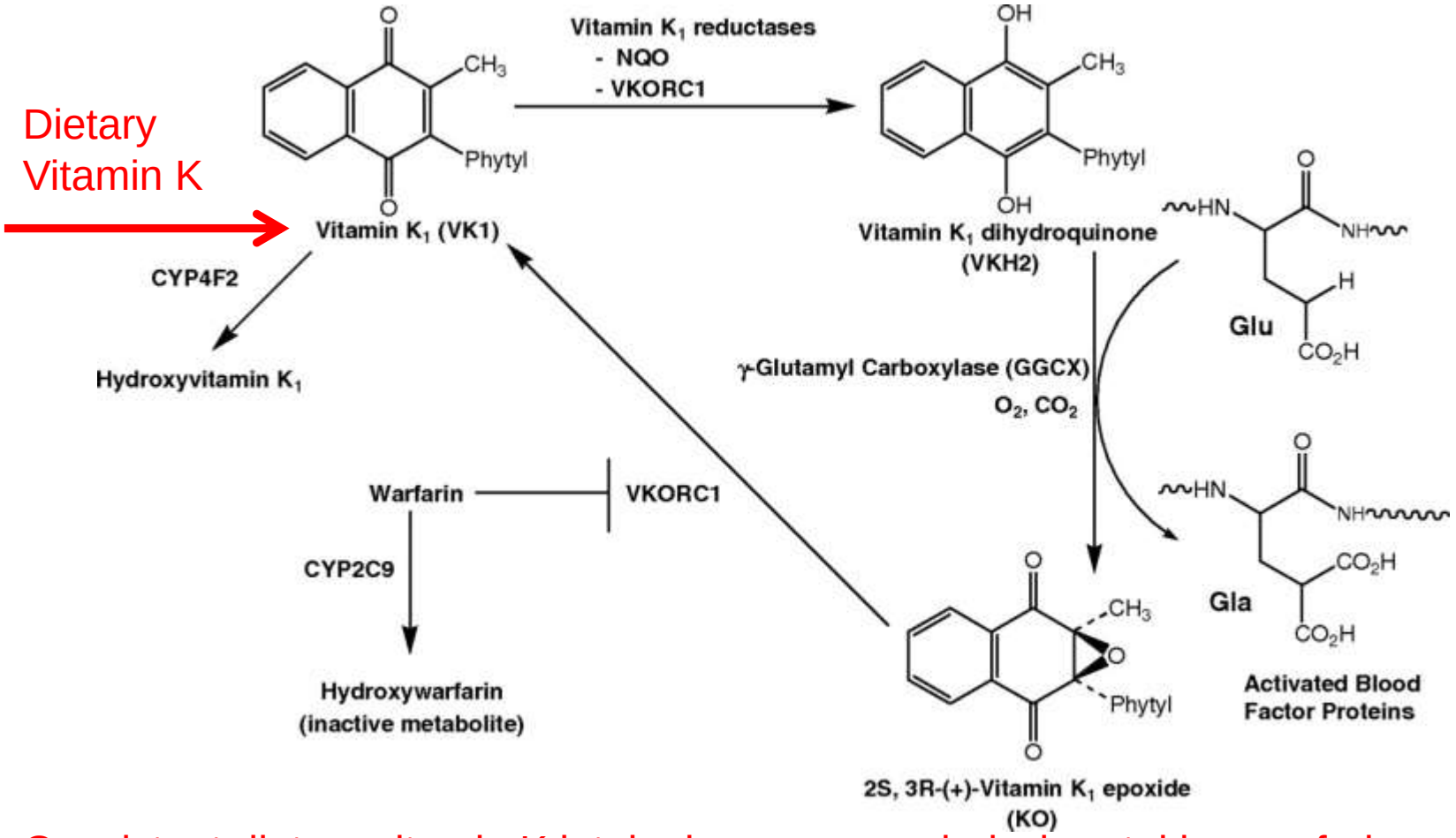
Warfarin: PGx and Dietary Vitamin K

Warfarin

- Anti-thrombotic agent
  - Inhibits vitamin K epoxide reductase (VKOR) complex
  - Synthesis of vitamin-K dependent clotting factors (II, V, VII, IX) is inhibited
  - Indicated in treatment and prophylaxis of venous and arterial thrombotic disorders
  - Substantial inter-individual variability in maintenance dose requirement exists (0.5 to 20 mg/day)
- **Narrow therapeutic index agent**
  - Monitor INR
  - Adverse event: bleeding

Courtesy of C. Lee

Warfarin Metabolism



Consistent dietary vitamin K intake is recommended when taking warfarin.

http://molpharm.aspetjournals.org/content/75/6/1337/F2.large.jpg

VKORC1 Alleles

Allele	Effect	Warfarin Dose Needed
-1639A	**Lower *VKORC1* expression *(i.e., less drug target to inhibit)***	**Lower dose**
-1639G	**Higher *VKORC1* expression**	**Higher dose**

Rieder et al. *NEJM* 2005

Population Frequencies of *VKORC1* alleles

-1639A

- Caucasian: 39%
- Black: 11%
- Asian: 91%

Courtesy of C. Lee

CPIC Guidelines for Warfarin

Table 1 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*	*CYP2C9*1/*2*	*CYP2C9*1/*3*	*CYP2C9*2/*2*	*CYP2C9*2/*3*	*CYP2C9*3/*3*
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.

- Wild-type (CYP2C9*1)
- 2 variant alleles (CYP2C9*2 and *3)

Johnson et al. *Clinical Pharmacology and Therapeutics,* 2011

The Genetic Intersection Between Nutrition and Pharmacy: The Potential for Better Disease Management in Hypertension

Hypertension (HTN) is a Major Public Health Concern

3 in 10 adults are pre-hypertensive

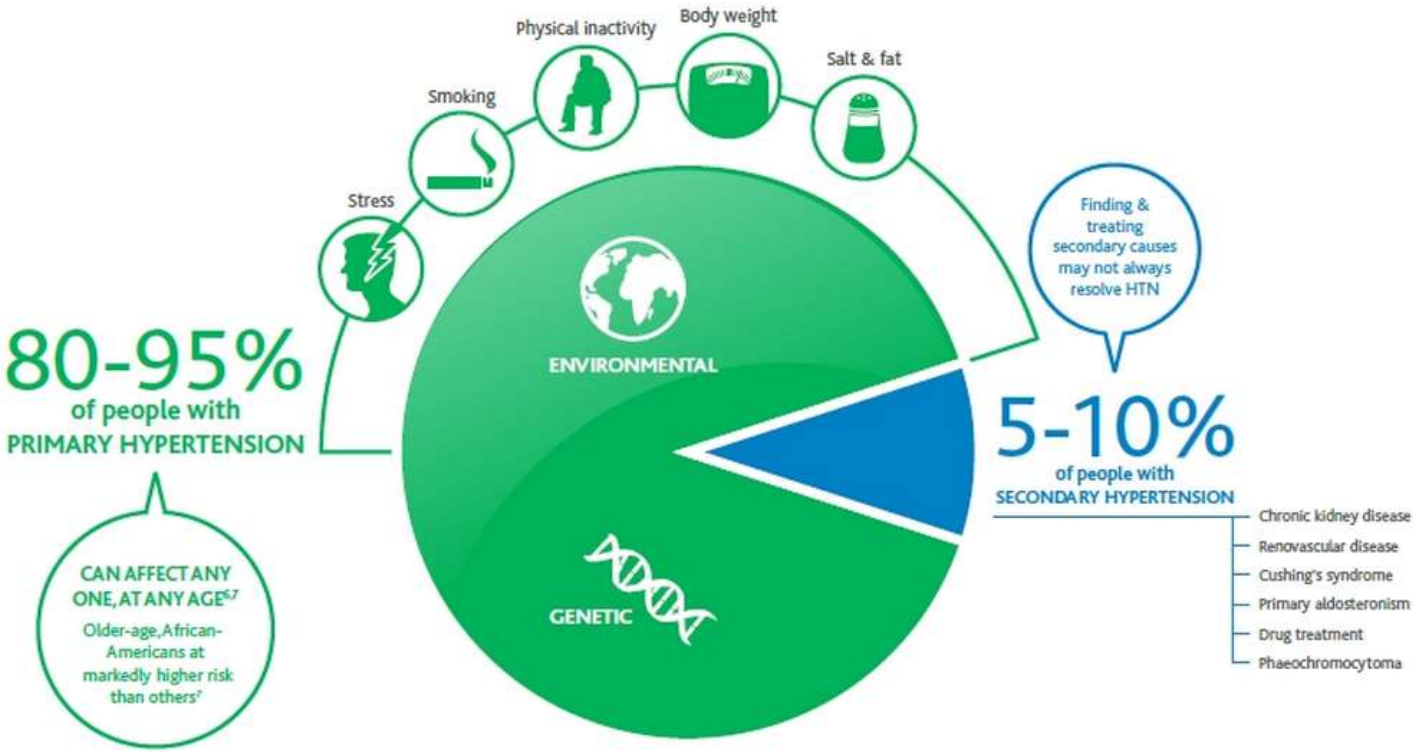
3 in 10 adults have HTN

1 in 2 adults with HTN DO NOT have their BP under control

- Increase risk of cardiovascular mortality with increasing BP
- HTN accounts for 54% of strokes and 47% of IHD
- Estimated lifetime risk of developing HTN is ~90%

(2015 Scientific Report of the 2015 Dietary Guidelines Advisory Committee, 2015 CDC Stroke Fact Sheet, Lawes et al. *Lancet*, 2008)

Causes and Risk Factors for HTN: Focusing on Salt Intake and Genetics

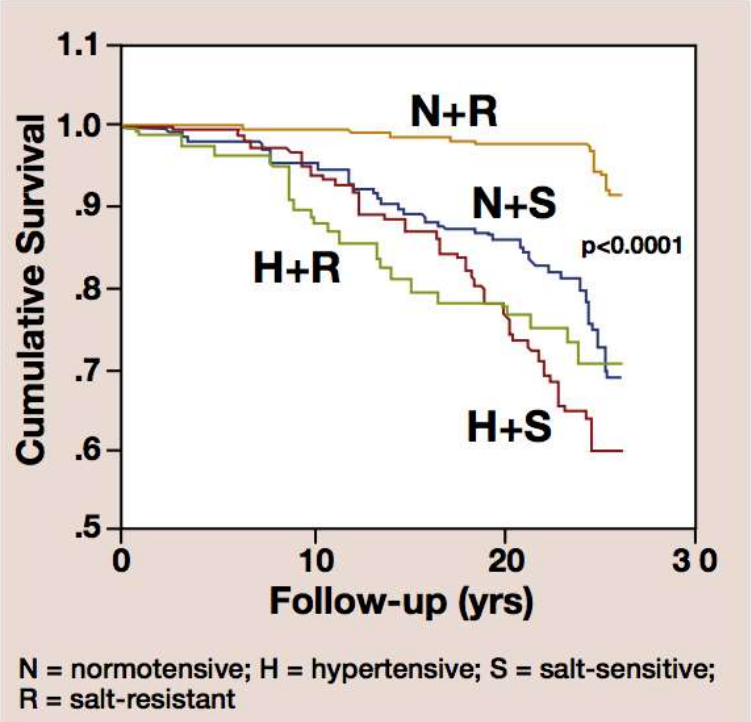


References: 1. Dosh SA. *J Fam Pract.* 2001;50:707–12. 2. Taler SJ. *Prim Care Clin Office Pract* 2008; 35: 489–500. 3. Calhoun DA, Jones D, Textor S, *et al. Hypertension* 2008; 51: 1403–19. 4. Pisoni R, Ahmed MI, Calhoun DA. *Curr Cardiol Rep.* 2009; 11: 407–13. 5. Rossi GP. *Curr Hypertens Rep.* 2010; 12: 342–348. 6. Liebson PR. *Prev Cardiol.* 2009; 12:189-97. 7. Levine DA, Lewis CE, Williams OD, *et al. Hypertension* 2011; 57:39-47.

What are the benefits of identifying the salt sensitive phenotype?

- Observational study
- Cohort of 708 subjects:
  - 278 with HTN
  - 338 salt sensitive
  - Followed for up to 27 years
- Salt sensitivity was found to be a significant risk factor for mortality

FIGURE 1. SALT SENSITIVITY REDUCES SURVIVAL IN NORMAL AND HYPERTENSIVE PARTICIPANTS



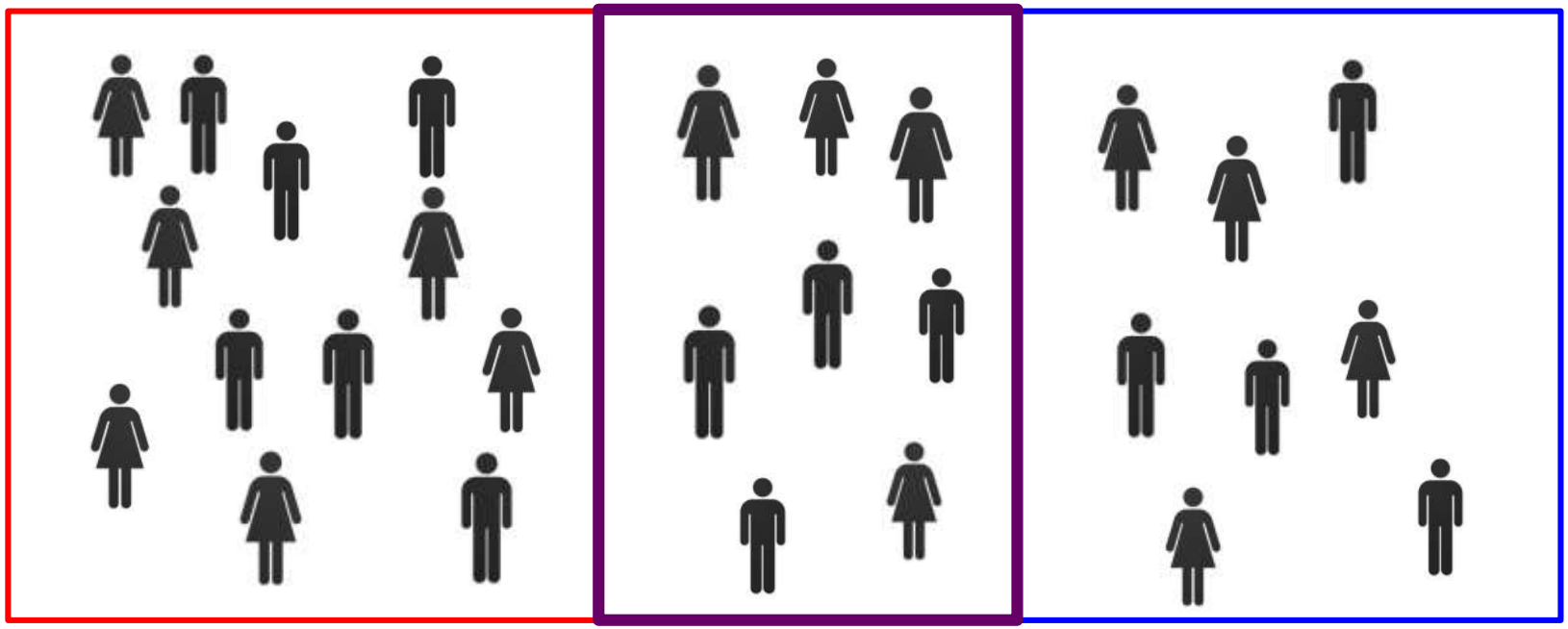
N = normotensive; H = hypertensive; S = salt-sensitive; R = salt-resistant

Weinberger et al., *Hypertension*, 2001

The Intersection Between Salt Sensitivity and Hypertension

Hypertensive (30.4%), 67 Million People

Salt Sensitive (26.4%), 58 Million People



Hypertensive & Salt Resistant (18%), 40 Million

Hypertensive & Salt Sensitive (12%) 26 Million

Normotensive & Salt Sensitive (14%), 31 Million

Felder et al., *Curr Opin Nephrol Hypertens*, 2013

Samples from Previously Published Cohort

- 55 HTN, 130 normotensive white subjects from UVA (discovery cohort)
- 211 white HTN subjects for the replication cohort
- Study looked at 17 candidate genes, 35 SNPs. 2 variants were associated with SS (2 in SLC4A5)
- Replication was confirmed in 2nd cohort
- SLC4A5 was significantly associated with SS in 2 separate white populations

Target Genes

Gene	Function
ADD1 exons	Gene responsible for the modulation activity of sodium transport systems. It increases renal tubular Na^+/K^+ ATPase activity. Variants in this gene result in greater blood pressure response when dietary sodium is varied. (Meneton et al. *Physiological Reviews,* 2005)
GRK4 exons	Polymorphisms cause hyperphosphorylation, desensitization, and internalization of the dopamine 1 receptor and increasing the expression of angiotensin type 1 receptor. Renal dopamine receptors are responsible for 50% of sodium excretion during moderate sodium excess. Polymorphisms in these receptors are linked to hypertension and salt sensitivity. (Robin et al*. Current Opinion in Nephrology and Hypertension,* 2013)
SLC4A5 exons	Gene codes for a protein that transports sodium and bicarbonate across the cell membrane in the distal nephron. Knocking out this transporter results in sodium retention and hypertension. (Felder et al. *Current Opinion in Nephrology and Hypertension,* 2013)

36 genes so far

Genes	Function
4. UMOD (2 SNPs)	Codes for uromodulin, the most abundant urinary protein and is secreted by epithelial cells lining the thick ascending limb of the loop of Henle in the kidney. Multiple GWAS studies have identified 2 promoter SNPs as independent susceptibility to CKD and hypertension. (Matteo et al. *Nature Medicine*, 2013)
5. AGT (6 SNPs)	Angiotensinogen is the precursor for the angiotensin peptides (e.g. angiotensin I, II, III). Angiotensin II is a potent constrictor of all blood vessels. This gene helps control blood pressure and variants have been shown to increase salt sensitivity. (Hunt et al. *American Journal of Hypertension*, 1999)
6. CYP11B2 (1 SNP)	Codes for an enzyme in the adrenal cortex responsible for the synthesis of mineralocorticoid aldosterone. Aldosterone is stimulated when angiotensin II or high potassium levels are present. This results in sodium retention and potassium excretion. Greater risk of salt sensitivity has been observed with variants in this gene. (Pamies-Andreu et al. *Journal of Human Hypertension*, 2003)
7. SGK1 (2 SNPs)	Gene plays a central role in regulating the epithelial sodium channels in the distal nephron. Variants in this gene are associated with salt sensitivity and hypertension. (Rao et al. *Journal of Human Hypertension*, 2012)
8. NEDD4L (2 SNPs)	Gene regulates epithelial sodium channels in the distal nephron. Variants in this gene is associated with increased blood pressure and salt sensitivity. (Dahlberg et al. *PLoS ONE*, 2007)

Key Points

- Response to salt varies.
- Salt sensitivity is an independent risk factor of mortality.
- Using genetics to differentiate the salt-sensitive phenotype has the potential to identify patients who would benefit from dietary interventions and pharmaceutical treatments.

Olivia Dong

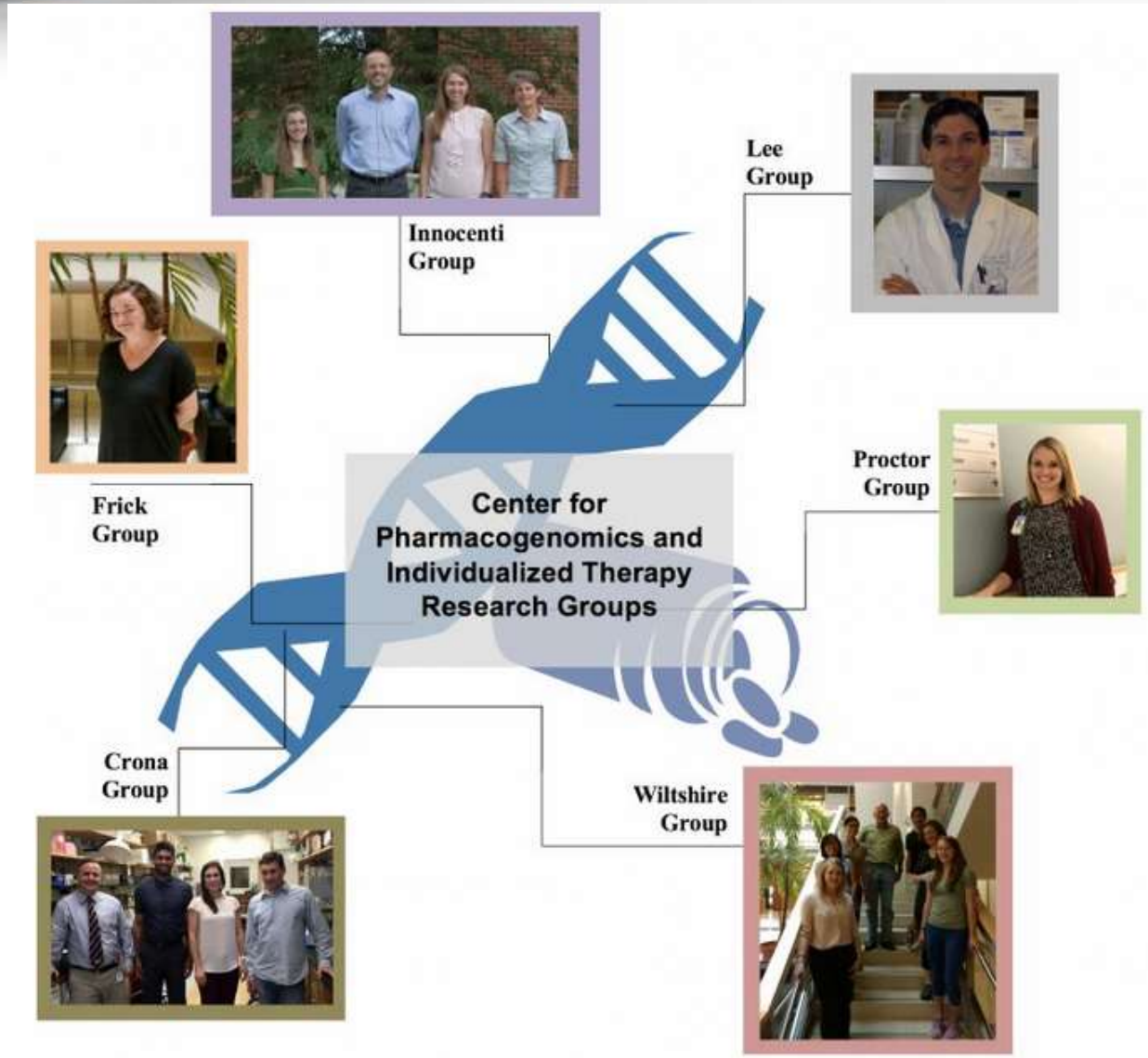
The Vision

"Here's my sequence..."

New Yorker, 2000

Perhaps you should know yours!

Questions?



- Dan Crona
- Amber Frick
- Federico Innocenti
- Craig Lee
- Amber Proctor
- Tim Wiltshire