



LABORATORY OF  
PERSONALIZED HEALTH



***Personalized Medicine in Real Time***

**DNA-Guided Clopidogrel (*Plavix*<sup>®</sup>) Management  
*Pharmacogenetic Foundations and Case Study***

# Clopidogrel (*Plavix*<sup>®</sup>)

## *Leading AntiPlatelet Drug*

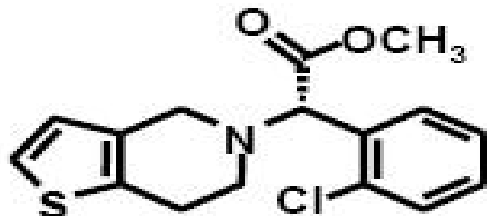
- Thienopyridine antiplatelet drug
- Irreversibly inhibits ADP receptor
- Marketed as *Plavix*<sup>®</sup>, Sanofi-Aventis/BMS
- Second largest selling drug in the world, \$9.5B sales 2008
- >22 million prescriptions issued in 2007
- Indicated to prevent death, MI, and stroke in patients with cardiovascular disease
- **Dosing:** Recent MI, stroke, PAD: 75 mg daily  
ACS: 300 mg x 1 → 75 mg daily



**Label Revision May 2009: Pharmacogenetics Section**  
*Variance on potency related to CYP2C19 gene polymorphisms*  
*Pharmacogenetic testing can identify genotypes of CYP2C19*

# Clopidogrel Activation to Metabolite

## *CYP2C19 Essential in Metabolite Formation*

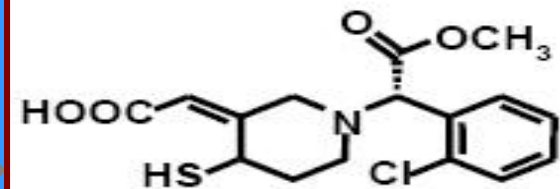


Clopidogrel

Clopidogrel

***ProDrug, Inactive***  
Requires metabolism  
by CYP2C19 for  
antiplatelet activity

**CYP2C19**



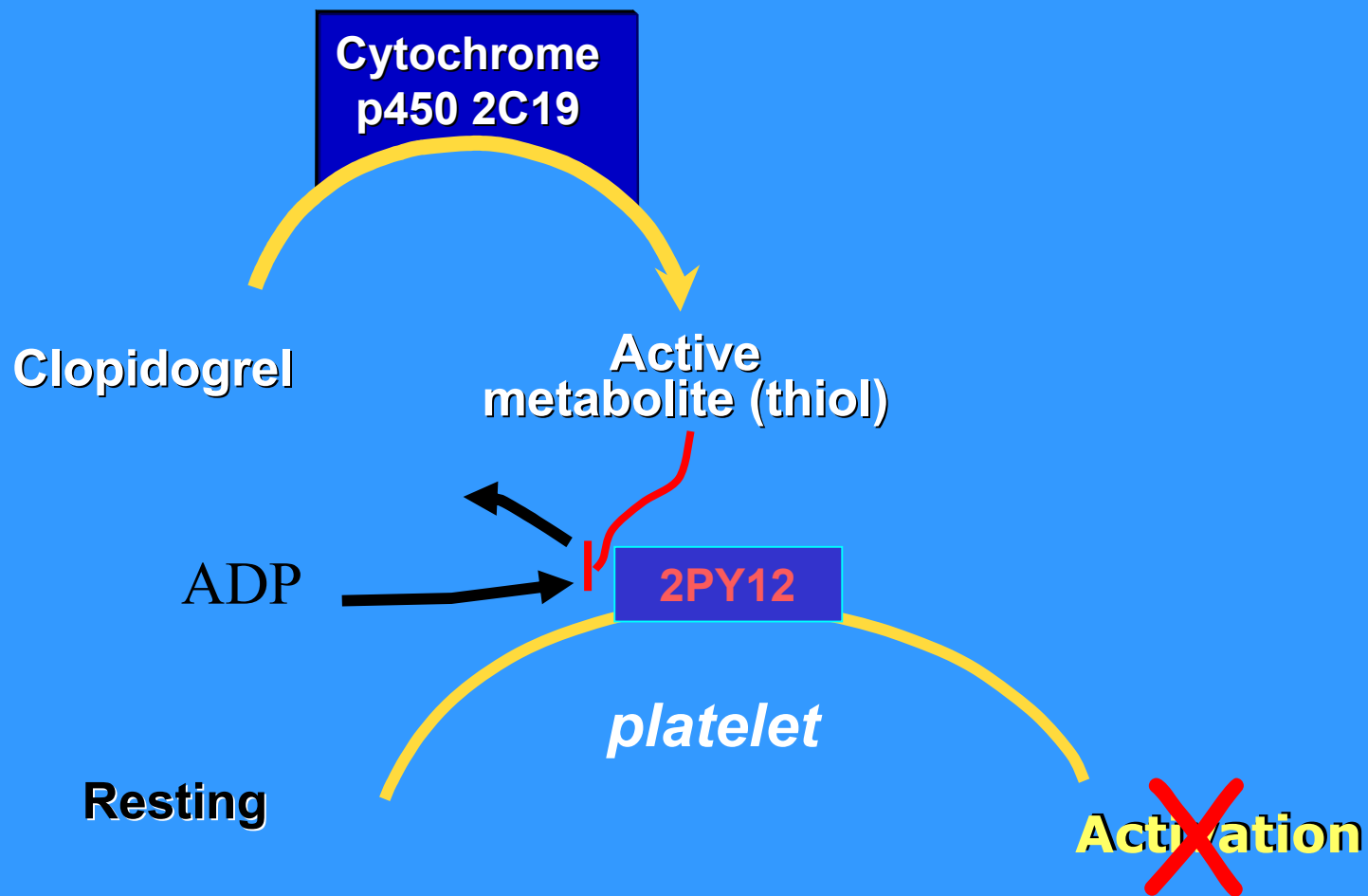
R-130964  
(active)

Active metabolite

***Metabolite, Active***  
Far more potent as  
P2Y<sub>12</sub> blocker than  
clopidogrel

# Clopidogrel Mechanism of Action

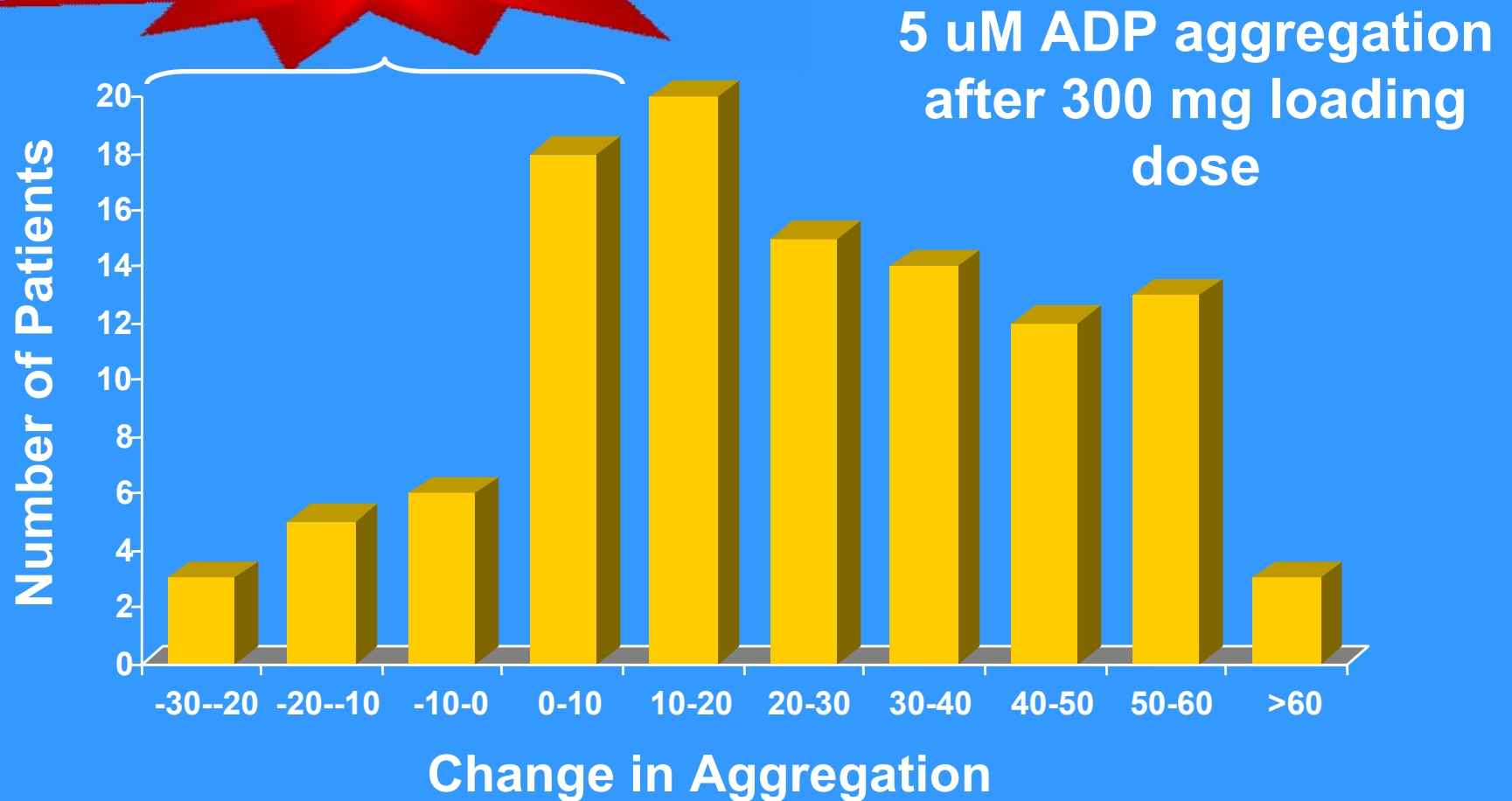
## *Pharmacokinetics and Pharmacodynamics*



# Clopidogrel Response

## Wide Range of Efficacy: Resistant Quartile

**"Resistance" = 31%**



# CYP2C19 Genotypes, Phenotypes

## 10 Alleles

green=Functional yellow=Deficient red=Null blue=Ultra

Allele	Change	Metabolizer Phenotype
*1	Reference	Functional
*2	Splicing defect	Null
*3	Stop codon	Null
*4	Start codon	Null
*6	Arg 132 Glu	Null
*7	Splicing defect	Null
*8	Trp 120 Arg	Null
*9	R 144 H	Deficient
*10	P 227 L	Deficient
*17	Promoter	Ultra

**Antidepressants**  
*Escitalopram (Lexapro®)*  
*Citalopram (Celexa®)*

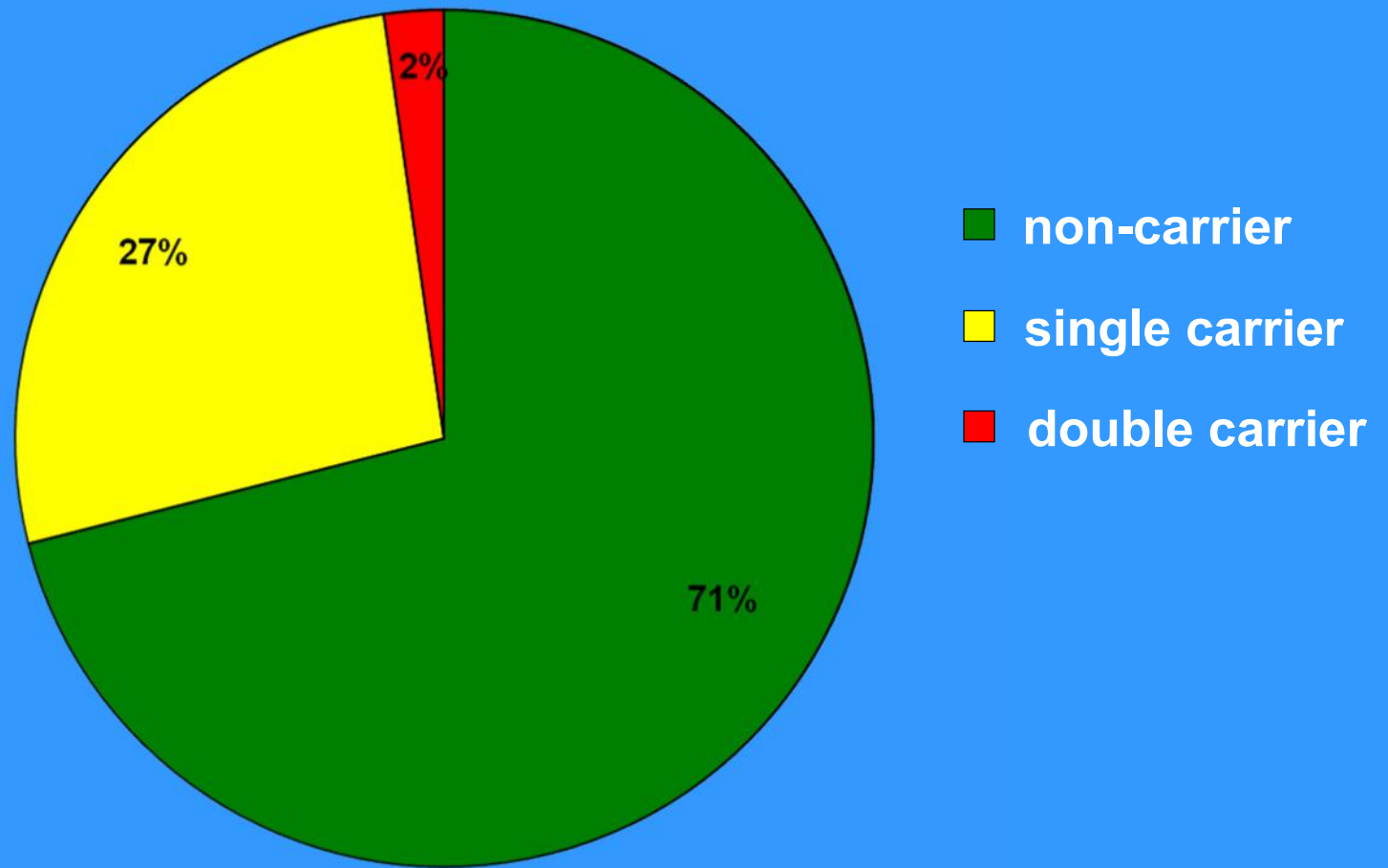
**Anti-epileptics**  
*Phenytoin (Dilantin®)*  
*Diazepam (Valium®)*

**Proton Pump Inhibitors**  
*Omeprazole (Prilosec®)*  
*Lansoprazol (Prevacid®)*  
*Esomeprazole (Nexium®)*

**AntiPlatelet ProDrug**  
*Clopidogrel (Plavix®)*

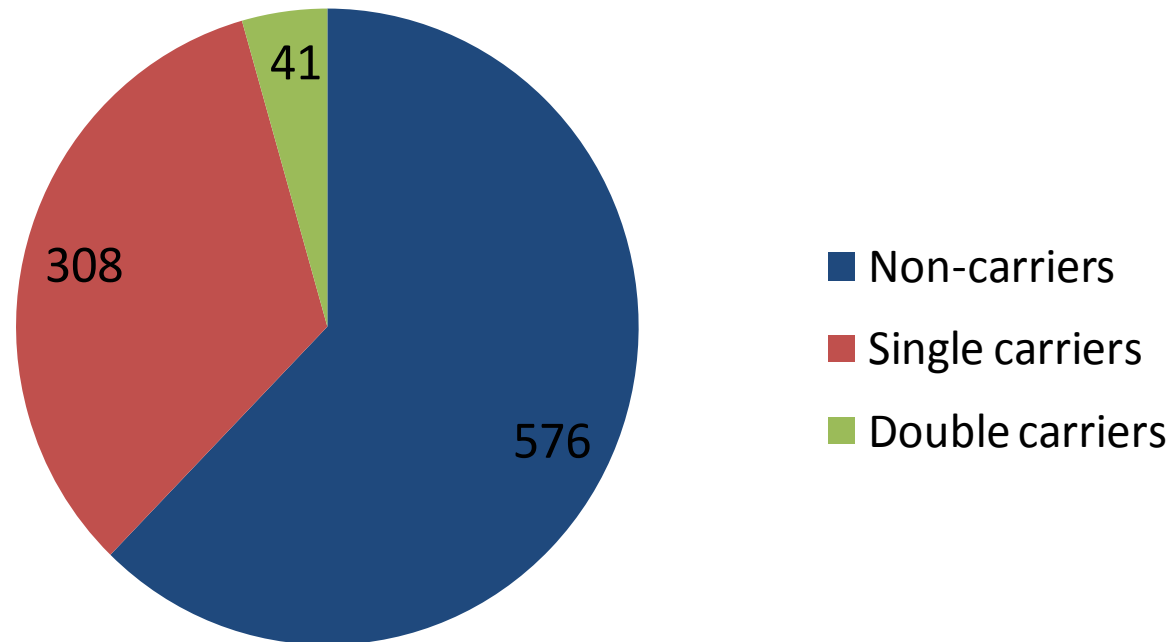
# CYP2C19 Carrier Status

*N=577 Referrals to Lab Personalized Health*



# Frequency of *CYP2C19* \*17 allele

## *Patients Referred: Pharmacogenetic Consult*



N = 925

Allele frequency = 21.1 %

Carrier frequency = 37.7%

HW p-value = 1.0 (perfect)



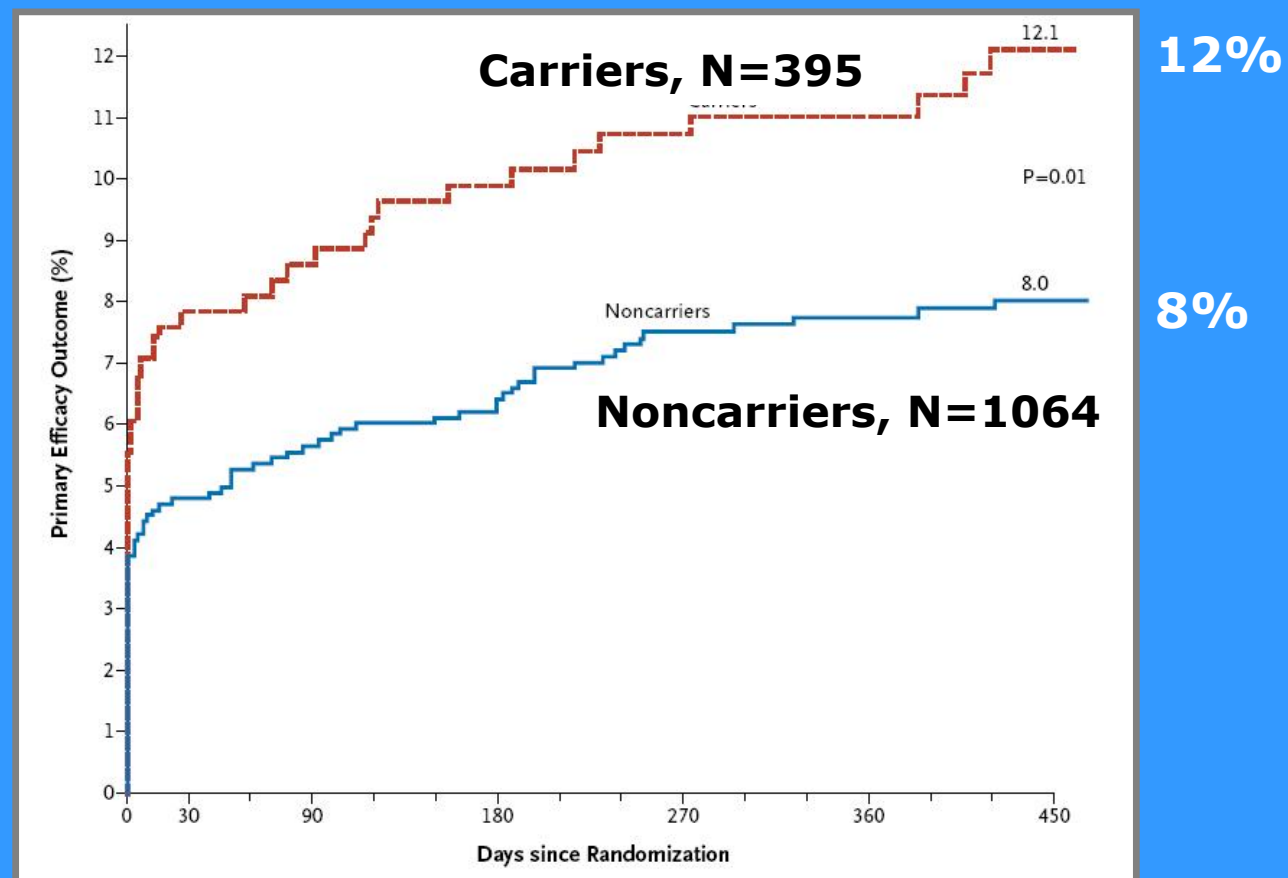
# CYP2C19 Genotypes, Phenotypes Population Frequencies

Allele	Genomic position (NCBI website‡)	Amino Acid Change or other effect	Enzymatic Activity	Frequency %					
				European	Asian	African	Native American	Oceania	Mixed Other
*1	wild-type	Reference		common	common	common	common	Not common	common
*2	19154 G>A	<i>Splicing defect</i>	Null	9-15	21-39	10-25	19	57	8-25
*3	17948 G>A	<i>Trp 212 X</i>	Null	0-2	0-13	0-2	0	25	0.1
*4	5001A>G	<i>Start codon</i>	Null	Rare	0.4	Rare	Rare	Rare	Rare
*5	19294 T>A	<i>Arg 433 Trp</i>	Null	Rare	Rare	Rare	Rare	Rare	Rare
*6	12748 G>A	<i>Arg 132 Glu</i>	Null	Rare	Rare	Rare	Rare	Rare	Rare
*7	19294 T>A	<i>Splicing defect</i>	Null	Rare	Rare	Rare	Rare	Rare	Rare
*8	12711 T>C	<i>Trp 120 Arg</i>	Null	Rare	Rare	Rare	Rare	Rare	Rare
*9	12784 G>A	<i>Arg 144 His</i>	Null	Rare	Rare	Rare	Rare	Rare	Rare
*10	19153 C>T	<i>Pro 227 Leu</i>	Decreased	Rare	Rare	Rare	Rare	Rare	Rare
<b>*17</b>	<b>4195C&gt;T</b>	<b>Promoter variant</b>	<b>Increased</b>	<b>18-27</b>	<b>1.4-4.0</b>	<b>19-24</b>	<b>?</b>	<b>?</b>	<b>?</b>

# Epidemiology CYP2C19 Polymorphisms

## *Association with Higher Event Rates*

### Death, MI, Stroke



12%

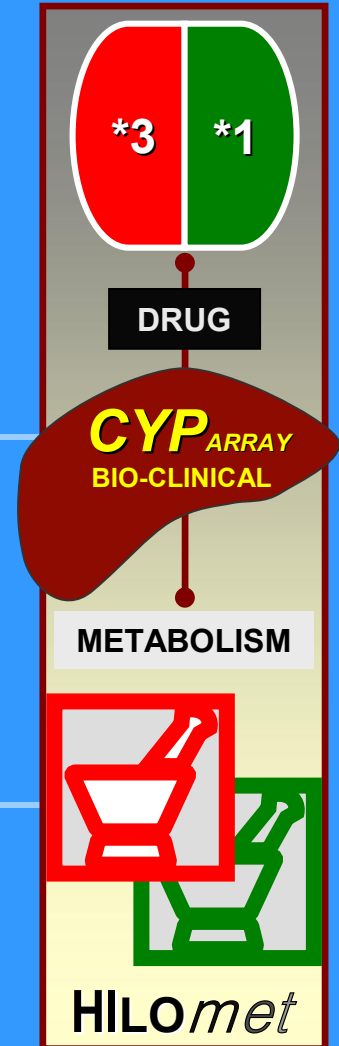
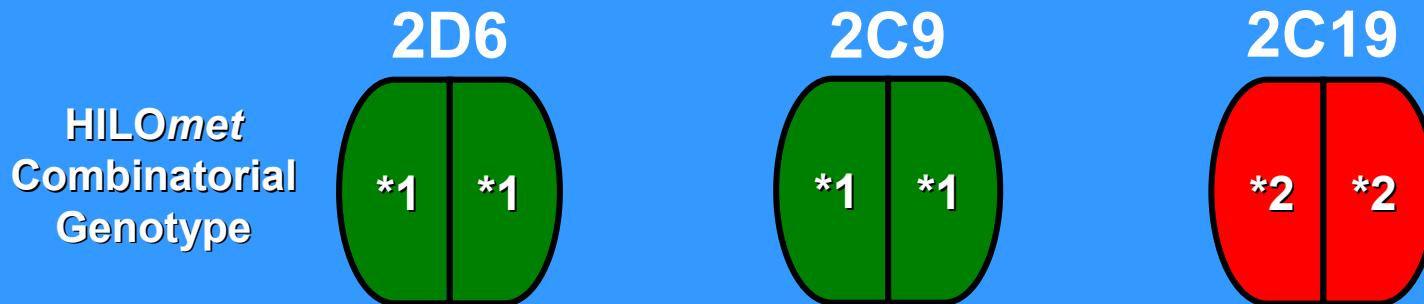
8%

# HILomet PhyzioType System: CTM3

## Case Report and Clinical Management Utility

*Patient CTM3 is a 74-year old Caucasian, diabetic man, hx. severe coronary arterial disease who manifested:*

**14 PTCAs, 7 stents, recurrent restenoses over 8 yrs; on clopidogrel 75 mg/d, high platelet reactivity**



Ruaño, Hirst, McKay et al, *Connecticut Medicine* 2012

# PHP Personalized Health Portal

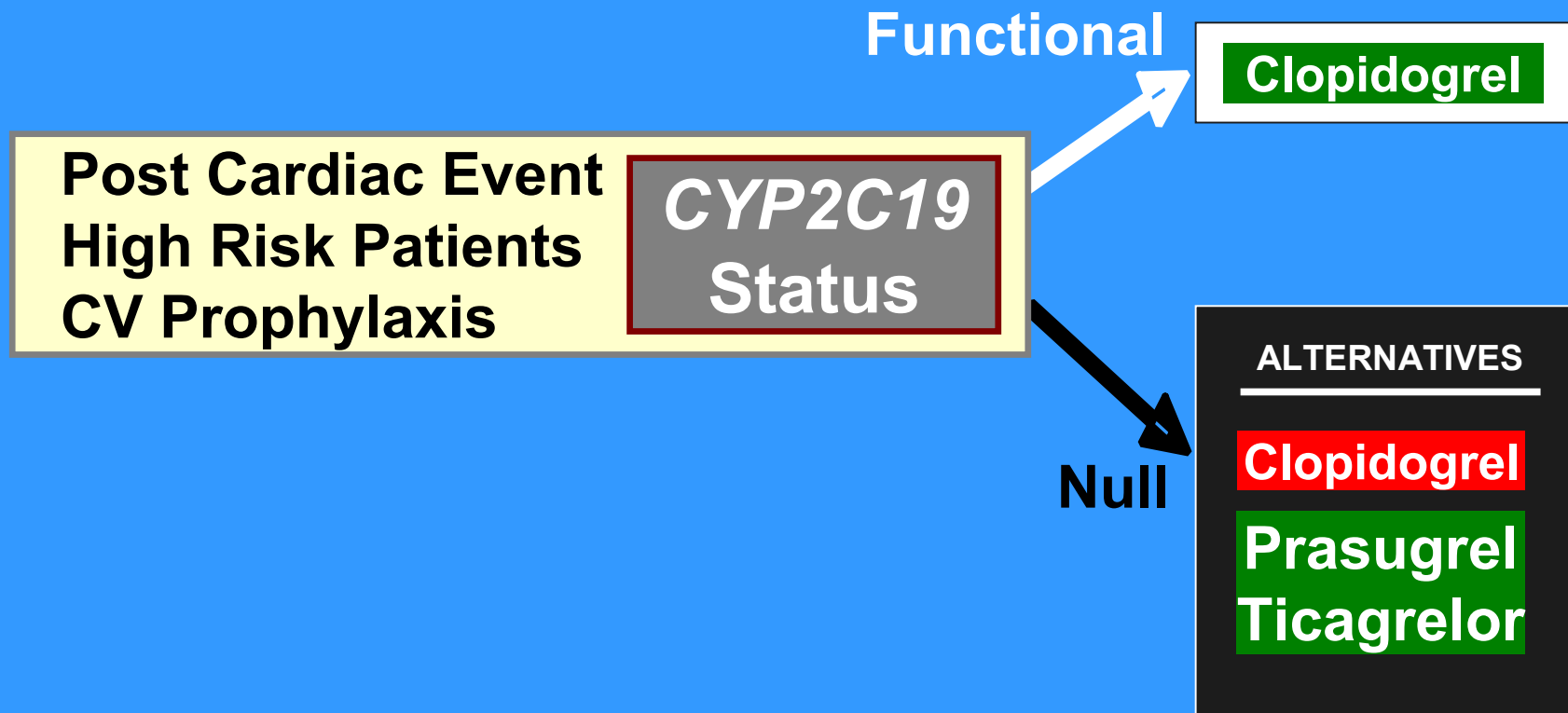
## Anti-Thrombotic Management: Patient CTM3

CYP2C19 Genotype	Antiplatelet Therapy Option to Consider
<b>*1/*1</b>	<b>Clopidogrel 75 mg/day</b>
<b>*1/*2, *1/*3</b>	<b>Clopidogrel 225 mg/day or Consider alternatives: Prasugrel 5 or 10 mg/day or Ticagrelor 90 mg/day, b.i.d.</b>
<b>*2/*2, *2/*3, *3/*3</b>	<b>Consider alternatives: Prasugrel 5 or 10 mg/day or Ticagrelor 90 mg, b.i.d.</b>
<b>*1/*17</b>	<b>Clopidogrel 75 mg/day with Rapid Effect</b>
<b>*2/*17, *3/*17</b>	<b>Consider alternatives: Prasugrel 5 or 10 mg/day or Ticagrelor 90 mg, b.i.d.</b>
<b>*17/*17</b>	<b>Clopidogrel 75 mg/day with Rapid Effect or Consider alternatives: Prasugrel 5 or 10 mg/day or Ticagrelor 90 mg, b.i.d.</b>

Note: Interpretations of the March 2010 clopidogrel label revision have become incorporated into recent clinical guidelines. Recommendations regarding patients heterozygous for null alleles call for supra-normal clopidogrel dosing levels.

# DNA-Guided Anti-Platelet Rx

## *CYP2C19 Individualized Decision Support*



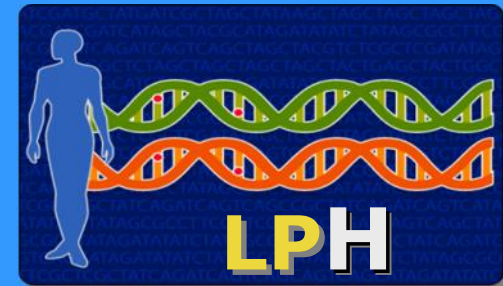
# ***LPH Laboratory of Personalized Health***

## ***CLP Clinical Lab Partners: CT Distributor***

- Pioneering high complexity pharmacogenetics laboratory + clinical practice
- Anchor for commercialization of **PhyzyoType Systems** throughout New England and nationally
- Referral Center for *Institute of Living + Mood Disorders Program*

- CT-wide CLP distribution and reimbursement agreement
- \$1.4M reimbursable revenue 2011
- Reimbursement rate  $\geq 95\%$
- 1044 Patients referred in 2011
- 3059 PhyzyoType tests in 2011
- Used by 206 Clinicians in 2011

### **LABORATORY OF PERSONALIZED HEALTH**



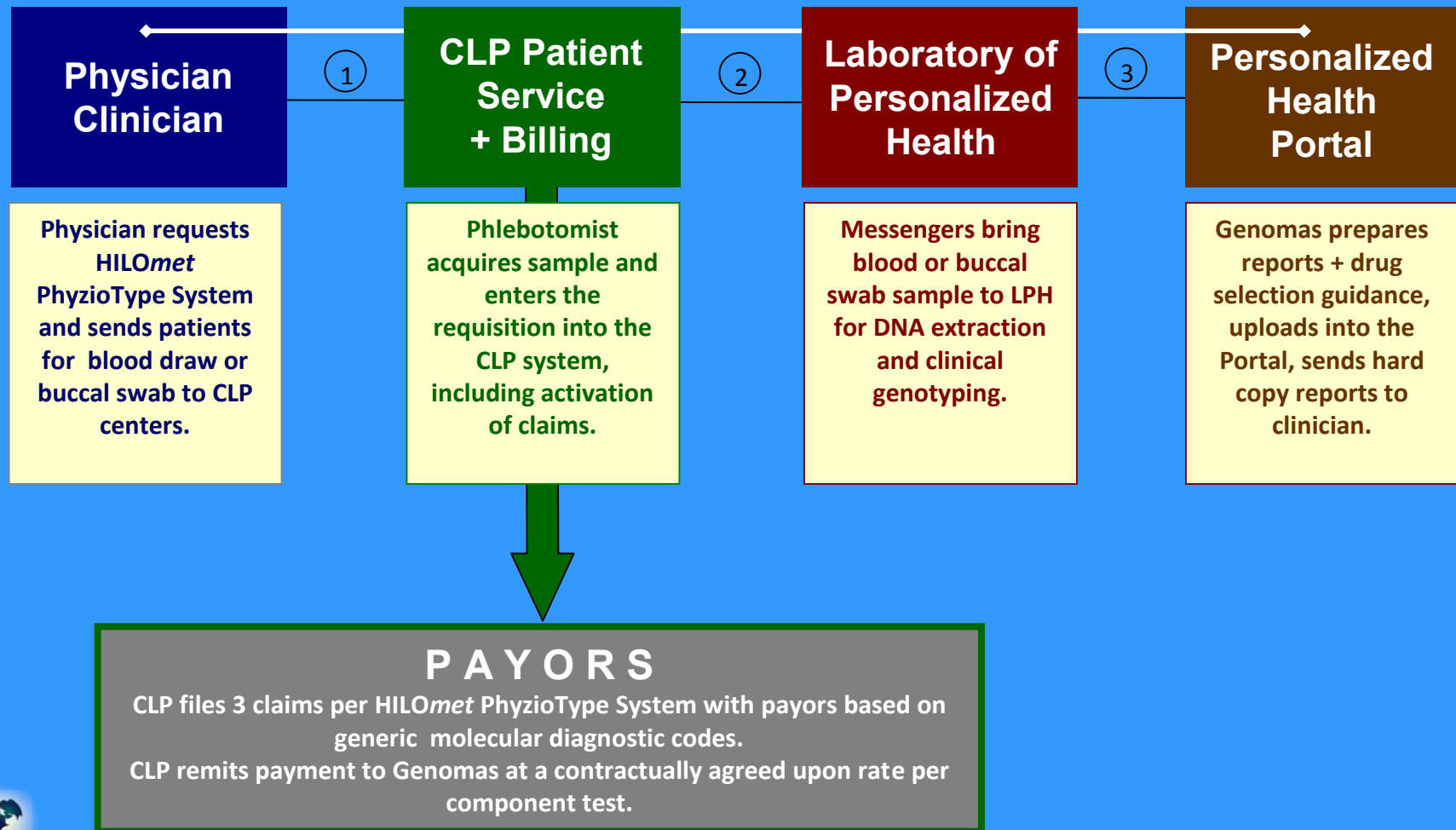
- Licensed by CT Dept of Public Health (#CL-0644) + R.I.
- CLIA certified and registered (Clinical Laboratory Improvement Amendments)
- ID #07D1036625 CMS (Centers for Medicare and Medicaid)
- 4 successful biannual inspections (most recent June 2011)



- 53 patient service centers in CT
- Subsidiary of Hartford Healthcare 14

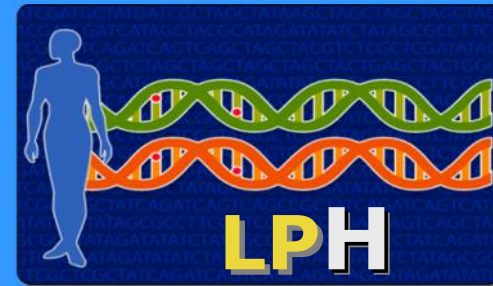
# *LPH Laboratory of Personalized Health*

## *CLIA Lab, Clinical Launchpad*





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**Thank You !**

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***LPH@genomas.net***

**860-545-4589**

**[www.genomas.com](http://www.genomas.com)**

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