Current Pharmacogenetics: Trends in Pharmacy Practice

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Disclosures

• I have no disclosures or relevant conflicting interests
Objectives

• Understand the history and principles of pharmacogenetics/genomics (PGx)

• Utilize PGx biomarkers that are currently available to personalize pharmacotherapy

• Utilize PGx educational resources that are available for pharmacists and health care practitioners

• Understand the future applications of PGx in personalized medicine
The Clinical Potential of PGx: Can We Increase The Responsiveness To Drugs?

Figure 2. Percentage of patients for whom drugs are ineffective. (Source of data: Spear, B.B., Heath-Chiozzi, M., & Huff, J. (2001). Clinical application of pharmacogenetics. *TRENDS in Molecular Medicine, 7*(5), 201-204.) (Note that lack of efficacy in a given patient may reflect a complex interaction of factors and can also result from inadequate or inappropriate dosing regimens of a drug that would otherwise be effective, as well as lack of adequate patient compliance.)
The Clinical Potential of PGx: Can We Increase The Responsiveness To Drugs?

Patients with same diagnosis

- Predicted good response to tested drug
- Predicted poor or nonresponse
  - Use different drug
- Predicted increased toxicity risk
  - Decrease dose or use different drug
Genetic Variability Influences Response to Pharmacotherapy
Genetic Variability Influences The Functionality of Targets of Pharmacotherapy

$\beta$-Adrenergic Receptor polymorphisms at codons 49 and 389 alter the properties of the receptor.
Polymorphisms in drug metabolizing enzymes can result in increased or decreased metabolism of drugs. The Pie charts below characterize the percentage of commonly used drugs that are metabolized by the respective enzymes.
Polymorphisms in transporters influence metabolism/clearance of commonly used drugs.
Pharmacogenomics

- Targets
- Transporters
- Metabolizing enzymes

Variability in Efficacy/Toxicity

Pharmacodynamics
Pharmacokinetics
Genomic Testing Costs: Decreasing Faster Than Predicted By Moore’s Law

The Decreasing Cost of Genotype Information.

Shown is an approximate timeline of milestones in genetics research that have been enabled by the corresponding decline in sequencing costs. Costs are shown as both actual costs and costs if they followed Moore’s law (which states that computing power doubles approximately every 2 years). Phenotyping costs are unknown but are assumed to have remained relatively flat as compared with the rapid drop in sequencing costs. Next-generation sequencing has reduced the cost and increased the resolution of genotype-phenotype correlations to the point where knowledge of genotype often drives discovery of phenotypic associations in a previously unexpected fashion. GWAS denotes genomewide association study, and NHLBI National Heart, Lung, and Blood Institute.
Genomic Testing Costs: Decreasing Faster Than Predicted By Moore’s Law

- We must be prepared to interpret PGx data that are published in package inserts of FDA approved drugs.
- We must also be prepared to interpret the results of PGx tests that are being directly marketed to patients.
Available PGx Resources

- FDA Center for Drug Evaluation and Research: Genomics Group
- NIH Funded Pharmacogenomics Research Network (PGRN) Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines
Link To FDA PGx Information

• http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/default.htm
Screen Shot of FDA Genomics

FDA Genomics

Sign up for free email updates about additions to the Genomics pages.

- Genomics Overview
- What's New and Upcoming Events
- Regulatory and Scientific Information
  - Guidelines, Concept Papers and MaPPs
  - Table of Valid Genomic Biomarkers in the Context of Approved Drug Label
  - Genomic Data Submission
  - Decision Tree for Genomic Data Submission
  - Voluntary Exploratory Data Submission (VXDS) (formerly Voluntary Genomic Data Submission (VGDS))
  - Quick Reference Guide
  - Interdisciplinary Pharmacogenomics Review Group (IPRG)
- Frequently Asked Questions
- Pharmacogenomics Education and Outreach Initiatives
- Drug Development and Drug Interactions
- Publications by FDA Staff
- Presentations
- Related Links
- Contact Information

Genomics Overview

Pharmacogenomics allows us to identify sources of an individual's profile of drug response and predict the best possible treatment option for this individual. The use of genomic information, accelerated by the sequencing of the human genome and the advent of new tools and technologies, has opened new possibilities in drug discovery and development. Consequently, regulatory science and regulations are set in place appropriately, as new scientific evidence is forthcoming.

FDA recognizes the importance of pharmacogenomics and encourages its use in drug development. This is reflected in the FDA white paper "Stagnation or Innovation? - Challenge and Opportunity on the Critical Path to New Medical Products," which identifies pharmacogenomics as a key opportunity for the Critical Path.
CPIC: Clinical Pharmacogenetics Implementation Consortium

The Clinical Pharmacogenetics Implementation Consortium (CPIC) was formed in late 2009, as a shared project between PharmGKB and the Pharmacogenomics Research Network. CPIC guidelines are peer-reviewed and published in a leading journal (in partnership with Clinical Pharmacology and Therapeutics) with simultaneous posting to PharmGKB with supplemental information/data and updates. Anyone with clinical interests in pharmacogenetics is eligible for membership. CPIC’s goal is to address some of the barriers to implementation of pharmacogenetic tests into clinical practice.

Questions? Send email to cpic@pharmgkb.org.

CPIC Team

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Pharmacogenomics

Variability in Efficacy/Toxicity

Targets
Transporters
Metabolizing Enzymes

Pharmacodynamics
Pharmacokinetics

Variability in Efficacy/Toxicity
Drug Targets
The likelihood of obtaining goal blood pressure with the first antihypertensive agent that is selected is approximately 50%.
Genetic Variability Influences The Functionality of Targets of Pharmacotherapy

β-Adrenergic Receptor polymorphisms at codons 49 and 389 alter the properties of the receptor.
Variant GLY389 Allele carriers have a blunted response to Metoprolol.

* $p < 0.01$

# $p < 0.002$

-16 -14 -12 -10 -8 -6 -4 -2 0
β-blocker Pharmacogenetics
S-metoprolol Concentrations Prove This Effect Was Due to the β-Adrenergic Receptor SNPs and not Pharmacokinetics
Commonly Used Pharmacotherapy in Heart Failure

- **Beta-blockers**
- **Digoxin, inotropes**
- **ACE inhibitors, angiotensin-receptor blockers, aldosterone antagonists**
- **Diuretics, aldosterone antagonists, nesiritide**
- **Peripheral arteries**

Copyright © 2003 Massachusetts Medical Society.
The β-Adrenergic Receptor polymorphisms may have been useful for identifying patients that would have benefitted from bucindolol. The drug initially failed clinical trials.
The β-Adrenergic Receptor polymorphisms carriers at codon 389 show no significant benefit from bucindolol while the wild type carriers had decreased hospitalization and increased survival.
Drug Target PGx Summary

• Genetic variation in the genes that produce the targets of drugs (i.e. Receptors, Enzymes, etc) can influence outcomes associated with pharmacotherapy
Drug Metabolism
Polymorphisms in drug metabolizing enzymes can result in increased or decreased metabolism of drugs. The Pie charts below characterize the percentage of commonly used drugs that are metabolized by the respective enzymes.
The Pharmacologic Response To Codeine: CYP2D6 and CYP3A4

**Figure 1** Codeine metabolism pathway in an individual with cytochrome P450 2D6 (CYP2D6) extensive metabolism. Asterisks (*) denote active metabolites.
Drug Metabolism Case Reports
CYP2D6 and Codeine

• Codeine is a commonly used pharmacologic agent in treatment of pain.

• Commonly prescribed as Tylenol # 3.

• Tylenol #3 is automatically ordered on many labor/delivery and surgery protocols at hospitals.
In April, 2005, a full-term healthy male infant, delivered vaginally, showed intermittent periods of difficulty in breastfeeding and lethargy starting on day 7. During a well-baby paediatric visit on day 11, the paediatrician noted that the baby had regained his birthweight. On day 12, however, he had grey skin and his milk intake had fallen. He was found dead on day 13. Postmortem analysis showed no anatomical anomalies. Blood concentration of morphine (the active metabolite of codeine) was 70 ng/mL by gas chromatography-mass spectrometry (GC-MS)—neonates breastfed by mothers receiving codeine typically have morphine serum concentrations of 0–2.2 ng/mL. The mother had been prescribed a combination preparation of codeine 30 mg and paracetamol 500 mg after birth for episiotomy pain (initially two tablets every 12 h, reduced to half that dose from day 2 because of somnolence and constipation). She continued the tablets for 2 weeks. Because of poor neonatal feeding, she stored milk on day 10, which was later assayed for morphine by GC-MS. A morphine concentration of 87 ng/mL was found—the typical range of milk concentrations after repeated maternal codeine is 1.9–20.5 ng/mL at doses of 60 mg every 6 h.
Genotype analysis was done for cytochrome P450 2D6 (CYP2D6), the enzyme catalysing the O-demethylation of codeine to morphine. The mother was heterozygous for a CYP2D6*2A allele with CYP2D6*2X2 gene duplication, classified as an ultra-rapid metaboliser. This genotype leads to increased formation of morphine from codeine, consistent with the somnolence and constipation she experienced. The maternal grandfather, the father, and the infant had two functional CYP2D6 alleles (CYP2D6*1/*2 genotypes), classified as extensive metabolisers. The maternal grandmother was an ultra-rapid metaboliser.

<table>
<thead>
<tr>
<th>Action</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid codeine when breastfeeding; use paracetamol or non-steroidal anti-inflammatory drugs</td>
<td>Avoids potential neonatal toxicity</td>
<td>Potential uncontrolled maternal pain</td>
</tr>
<tr>
<td>Avoid high-dose codeine (240 mg daily) for more than a few days</td>
<td>Minimises potential neonatal toxicity</td>
<td>Suboptimal maternal pain control</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose may still be too high a dose for ultra-rapid metabolisers</td>
</tr>
<tr>
<td>Avoid breastfeeding when taking codeine</td>
<td>Avoids potential neonatal toxicity</td>
<td>Loss of the benefits of breastfeeding</td>
</tr>
<tr>
<td>Inform and monitor mother and baby for signs of opioid toxicity</td>
<td>Ability to intervene early and prevent serious toxicity</td>
<td>Parental anxiety and false positive identification of toxicity</td>
</tr>
<tr>
<td>Genotype mother for CYP2D6</td>
<td>Predicts mothers at risk of producing excess of morphine</td>
<td>Expensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not presently routine</td>
</tr>
</tbody>
</table>

Table: Clinical strategies to manage breastfeeding while on codeine

KR Crews¹, A Gaedigk²,³, HM Dunnenberger¹, JS Leeder²,³, TE Klein⁴, KE Caudle¹, CE Haidar¹, DD Shen⁵,⁶, JT Callaghan⁷,⁸, S Sadhasivam⁹,¹⁰, CA Prows¹¹,¹², ED Kharasch¹³ and TC Skaar⁷
### Table 1 Assignment of likely codeine metabolism phenotypes based on cytochrome P450 2D6 (CYP2D6) diplotypes

<table>
<thead>
<tr>
<th>Likely phenotypea</th>
<th>Activity score</th>
<th>Genotypes</th>
<th>Examples of diplotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrarapid metabolizer (≈1–2% of patients)</td>
<td>&gt;2.0</td>
<td>An individual carrying more than two copies of functional alleles</td>
<td>*1/*1xN, *1/*2xN</td>
</tr>
<tr>
<td>Extensive metabolizer (≈77–92% of patients)</td>
<td>1.0–2.0b</td>
<td>An individual carrying two alleles encoding full or reduced function; or one full-function allele together with either one nonfunctional or one reduced-function allele</td>
<td>*1/*1, *1/*2, *2/*2, *1/*41, *1/*4, *2/*5, *1/*10</td>
</tr>
<tr>
<td>Intermediate metabolizer (≈2–11% of patients)</td>
<td>0.5b</td>
<td>An individual carrying one reduced-function and one nonfunctional allele</td>
<td>*4/*10, *5/*41</td>
</tr>
<tr>
<td>Poor metabolizer (≈5–10% of patients)</td>
<td>0</td>
<td>An individual carrying no functional alleles</td>
<td>*4/*4, *4/*5, *5/*5, *4/*6</td>
</tr>
</tbody>
</table>

*The frequency estimates are based on data from Caucasians and may differ substantially for other ethnicities. See Supplementary Data online for estimates of phenotype frequencies among different ethnic/geographic groups. bNote that some investigators define patients with an activity score of 0.5 and 1.0 as intermediate metabolizers and those with an activity score of 1.5 and 2.0 as extensive metabolizers. Classifying patients with an activity score of 1.0 as extensive metabolizers in this guideline is based on data specific for formation of morphine from codeine in these patients.12
### Table 2  Codeine therapy recommendations based on cytochrome P450 2D6 (CYP2D6) phenotype

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Implications for codeine metabolism</th>
<th>Recommendations for codeine therapy</th>
<th>Classification of recommendation for codeine therapy</th>
<th>Considerations for alternative opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrarapid metabolizer</td>
<td>Increased formation of morphine following codeine administration, leading to higher risk of toxicity</td>
<td>Avoid codeine use due to potential for toxicity.</td>
<td>Strong</td>
<td>Alternatives that are not affected by this CYP2D6 phenotype include morphine and nonopioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity.</td>
</tr>
<tr>
<td>Extensive metabolizer</td>
<td>Normal morphine formation</td>
<td>Use label-recommended age- or weight-specific dosing.</td>
<td>Strong</td>
<td>—</td>
</tr>
<tr>
<td>Intermediate metabolizer</td>
<td>Reduced morphine formation</td>
<td>Use label-recommended age- or weight-specific dosing. If no response, consider alternative analgesics such as morphine or a nonopioid.</td>
<td>Moderate</td>
<td>Monitor tramadol use for response.</td>
</tr>
<tr>
<td>Poor metabolizer</td>
<td>Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief</td>
<td>Avoid codeine use due to lack of efficacy.</td>
<td>Strong</td>
<td>Alternatives that are not affected by this CYP2D6 phenotype include morphine and nonopioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity; these agents should be avoided.</td>
</tr>
</tbody>
</table>

*Rating scheme is described in Supplementary Data online. There is substantial evidence for decreased efficacy of tramadol in poor metabolizers and a single case report of toxicity in an ultrarapid metabolizer with renal impairment following tramadol use postsurgery. Use of other analgesics in CYP2D6 poor and ultrarapid metabolizers may therefore be preferable. Some other opioid analgesics, such as hydrocodone and oxycodone, are metabolized by CYP2D6. To avoid treatment complications, opioids that are not metabolized by CYP2D6, including morphine, oxymorphone, buprenorphine, fentanyl, methadone, and hydromorphone, along with nonopioid analgesics, may be considered as alternatives for use in CYP2D6 poor and ultrarapid metabolizers.*
A Case of Respiratory Depression in a Child With Ultrarapid CYP2D6 Metabolism After Tramadol

Gilles Orliaguet, MD, PhD, Jamil Hamza, MD, PhD, Vincent Couloigner, MD, PhD, Françoise Denoyelle, MD, PhD, Marie-Anne Loriot, MD, PhD, Franck Broly, MD, PhD, Erea Noel Garabedian, MD

We discuss a case of severe respiratory depression in a child, with ultrarapid CYP2D6 genotype and obstructive sleep apnea syndrome, after taking tramadol for pain relief related to a day-case tonsillectomy.


DOI: 10.1542/peds.2014-2673

Accepted for publication Dec 8, 2014
The Pharmacologic Response To Tramadol: CYP2D6 Variation Influences Outcomes

- PGRN PK Pathway
- O-Desmethyl Tramadol is the primary metabolite from CYP2D6
  - O-Desmethyl Tramadol has 200 times more affinity for the MOR than the parent drug and other metabolites

• PGRN PK Pathway
• O-Desmethyl Tramadol is the primary metabolite from CYP2D6
• O-Desmethyl Tramadol has 200 times more affinity for the MOR than the parent drug and other metabolites
Respiratory Depression with Tramadol in a Patient with Renal Impairment and CYP2D6 Gene Duplication

Ulrike M. Stamer, MD*
Frank Stüber, MD*
Thomas Muders, MD*
Frank Musshoff, PhD†

We observed opioid-related respiratory depression in a patient receiving tramadol via patient-controlled analgesia. Predisposing factors were the patient’s genetic background and renal impairment. Complete recovery occurred after naloxone administration, thus confirming opioid intoxication. Analysis of the patient’s genotype revealed a CYP2D6 gene duplication resulting in ultra-rapid metabolism of tramadol to its active metabolite (+)O-desmethyltramadol. Concomitant renal impairment resulting in decreased metabolite clearance enhanced opioid toxicity. This genetic CYP2D6 variant is particularly common in specific ethnic populations and should be a future diagnostic target whenever administration of tramadol or codeine is anticipated, as both drugs are subject to a comparable CYP2D6-dependent metabolism.

(Anesth Analg 2008;107:926-9)
66 Year Old CYP2D6 Ultra-Metabolizer Case Report

Figure 1. Time course of tramadol treatment: The panels give information on (a) tramadol loading doses during surgery and in the PACU (postanesthesia care unit) and delivered patient-controlled analgesia (PCA) doses, (b) pain scores at rest and movement numeric rating scale (NRS 0–100), (c) plasma concentrations of (+)- and (−)-tramadol, and (d) plasma concentrations of (+)- and (−)-O-desmethyl tramadol (ODT). The table beneath summarizes vital values and sedation scores (1 = patient awake, spontaneous communication possible 2 = patient sleepy, but able to communicate 3 = patient sedated, but easily to awake 4 = patient severely sedated, but arousable by intense stimuli 5 = patient not arousable). At time point "0" the initial intraoperative tramadol loading dose was administered. Respiratory depression occurred 10.5 h after the initial loading dose and 6.5 h after the last PCA dose. BP = blood pressure.
Polymorphisms in transporters influence metabolism/clearance of commonly used drugs.
Statin Pharmacogenomics:
GWAS Analyses Identify OAT1B1 (SLC01B1)
Statin-Induced Myopathy

SLCO1B1 Variants and Statin-Induced Myopathy —
A Genomewide Study

The SEARCH Collaborative Group*
Statin Pharmacogenomics: GWAS Analyses Identify OAT1B1 (SLC01B1) Statin-Induced Myopathy

**Figure 1.** Results of Tests for a Trend in the Association between Myopathy and Each SNP Measured in the Genome-wide Association Study.

P values are shown for each SNP measured among 85 participants with myopathy and 90 matched controls who were taking 80 mg of simvastatin daily. Analyses are based on 316,184 of the 318,237 SNPs (99.4%) on the Sentrix HumanHap300-Duo BeadChip (Illumina). A result above the horizontal red line indicates strong evidence of an association (P<5×10⁻⁷).
Statin Pharmacogenomics: GWAS Analyses Identify OAT1B1 (SLC01B1) Statin-Induced Myopathy
The OAT1B1 (SLCO1B1 polymorphism results in increased Simvastatin concentrations in muscles of patients and ultimately increased occurrences of myopathy.

<table>
<thead>
<tr>
<th>SLCO1B1 c.521T&gt;C genotype</th>
<th>Normal dose range*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT</td>
<td>80 mg</td>
</tr>
<tr>
<td>TC</td>
<td>4 mg</td>
</tr>
<tr>
<td>CC</td>
<td>80 mg</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>80 mg</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>80 mg</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>80 mg</td>
</tr>
</tbody>
</table>

![Graph showing Simvastatin concentration over time for different genotypes.](#)

![Graph showing cumulative percentage of patients with myopathy over years since starting Simvastatin.](#)

![Graph showing Simvastatin acid levels for different SLCO1B1 genotypes.](#)

doi:10.1038/clpt.2009.197
### Table 1  Assignment of likely SLCO1B1 phenotype based on genotype

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Genotype definition</th>
<th>Examples of diplotypes</th>
<th>Genotype at rs4149056</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal function; homozygous wild type or normal</td>
<td>An individual carrying two normal-function alleles</td>
<td>*1a/*1a, *1a/*1b, *1b/*1b</td>
<td>TT</td>
</tr>
<tr>
<td>(55–88% of patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate function; heterozygous</td>
<td>An individual carrying one normal-function allele plus one decreased-function allele</td>
<td>*1a/*5, *1a/*15, *1a/*17, *1b/*5, *1b/*15, *1b/*17</td>
<td>TC</td>
</tr>
<tr>
<td>(11–36% of patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low function; homozygous variant or mutant</td>
<td>An individual carrying two decreased-function alleles</td>
<td>*5/*5, *5/*15, *5/*17, *15/*15, *15/*17, *17/*17</td>
<td>CC</td>
</tr>
<tr>
<td>(0–6% of patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Frequency of the polymorphism varies by ancestral group (Supplementary Tables S3 and S4 online).
Table 2  Dosing recommendations for simvastatin based on SLCO1B1 phenotype

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Implications for simvastatin</th>
<th>Dosing recommendations for simvastatin&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Classification of recommendations&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal function</td>
<td>Normal myopathy risk</td>
<td>Prescribe desired starting dose&lt;sup&gt;b&lt;/sup&gt; and adjust doses of simvastatin based on disease-specific guidelines</td>
<td>Strong</td>
</tr>
<tr>
<td>Intermediate function</td>
<td>Intermediate myopathy risk</td>
<td>Prescribe a lower dose or consider an alternative statin (e.g., pravastatin or rosuvastatin); consider routine CK surveillance</td>
<td>Strong</td>
</tr>
<tr>
<td>Low function</td>
<td>High myopathy risk</td>
<td>Prescribe a lower dose or consider an alternative statin (e.g., pravastatin or rosuvastatin); consider routine CK surveillance</td>
<td>Strong</td>
</tr>
</tbody>
</table>

CK, creatine kinase.

<sup>a</sup>In all cases, the potential for drug–drug interaction should be evaluated before initiating a prescription. <sup>b</sup>The US Food and Drug Administration recommends against 80 mg (unless already tolerated for 12 months). <sup>c</sup>See the Supplementary Material online (text section titled “Levels of Evidence”) for additional details regarding the three-tiered system used to grade the quality of evidence.
Drug Metabolism PGx Summary

• Genetic variation in the genes that produce the drug metabolism enzymes and drug transporters can influence outcomes associated with pharmacotherapy.

• We have recently witnessed mandated changes in prescribing and many PGx guidelines that are linked to genetic variation in drug metabolism.
PGx Implementation

• Do we have any examples of the implementation of PGx into clinical practice? Yes

• Clopidogrel is a perfect example, so we will review the University of Florida Personalized Medicine Program’s (UF PMP) published data
Plavix (Clopidogrel)

(Pharmacotherapy 2010;30(3):265–274)
Plavix (Clopidogrel) and CYP2C19

A Pharmacokinetic Response

<table>
<thead>
<tr>
<th>Gene</th>
<th>Percent Difference in AUC₀₋₁</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19</td>
<td>-32.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>-6.8</td>
<td>0.59</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>-15.7</td>
<td>0.03</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>5.6</td>
<td>0.59</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>11.2</td>
<td>0.45</td>
</tr>
</tbody>
</table>

B Pharmacodynamic Response

<table>
<thead>
<tr>
<th>Gene</th>
<th>Absolute Difference in ΔMPA</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19</td>
<td>-9.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>-0.6</td>
<td>0.86</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>-5.7</td>
<td>0.012</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>7.5</td>
<td>0.012</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>0.5</td>
<td>0.90</td>
</tr>
</tbody>
</table>
Plavix (Clopidogrel) and CYP2C19

**Graph A: Primary Efficacy Outcome**
- X-axis: Days since Randomization
- Y-axis: Primary Efficacy Outcome (%)
- Two lines: Carriers and Noncarriers
- Carriers: 12.1% at 450 days
- Noncarriers: 8.0% at 450 days
- P-value: 0.01
- No. at Risk:
  - Noncarriers: 1064, 1099, 999, 870, 755, 542

**Graph B: Start Thrombosis**
- X-axis: Days since Randomization
- Y-axis: Definite or Probable Start Thrombosis (%)
- Two lines: Carriers and Noncarriers
- Carriers: 2.6% at 450 days
- Noncarriers: 0.8% at 450 days
- P-value: 0.02
- No. at Risk:
  - Carriers: 375, 368, 366, 359, 316, 279
  - Noncarriers: 1014, 1004, 1001, 989, 885, 765, 547

**Table**
- Carriers of Reduced-Function Allele
- Carriers of Nonreduced Function Allele
- Hazard Ratio (95% CI)
- P-value

<table>
<thead>
<tr>
<th>Gene</th>
<th>Carriers of Reduced-Function Allele</th>
<th>Carriers of Nonreduced Function Allele</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19</td>
<td>16/235 (6.8)</td>
<td>83/1064 (8.0)</td>
<td>1.53 (2.07-2.19)</td>
<td>0.01</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>22/210 (10.5)</td>
<td>107/1226 (8.8)</td>
<td>1.09 (0.69-1.73)</td>
<td>0.41</td>
</tr>
<tr>
<td>CYP2C8</td>
<td>38/370 (10.5)</td>
<td>68/777 (9.0)</td>
<td>1.11 (0.76-1.62)</td>
<td>0.78</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>99/1130 (8.7)</td>
<td>14/131 (10.3)</td>
<td>0.89 (0.51-1.52)</td>
<td>0.69</td>
</tr>
<tr>
<td>CYP2A2</td>
<td>5/55 (9.5)</td>
<td>95/1099 (8.9)</td>
<td>0.97 (0.40-2.23)</td>
<td>0.96</td>
</tr>
</tbody>
</table>
Plavix (Clopidogrel) and CYP2C19

N ENGL J MED 10.1056/NEJMoa0808227
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PLAVIX safely and effectively. See full prescribing information for PLAVIX.

PLAVIX (clopidogrel bisulfate) tablets
Initial U.S. Approval: 1997

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)

FULL PRESCRIBING INFORMATION

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS
The effectiveness of Plavix is dependent on its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 [see Warnings and Precautions (5.1)]. Plavix at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with Plavix at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy [see Clinical Pharmacology (12.5)]. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers [see Dosage and Administration (2.3)].

WARNINGS AND PRECAUTIONS

- Reduced effectiveness in impaired CYP2C19 function: Avoid concomitant use with drugs that inhibit CYP2C19 (e.g., omeprazole). (5.1)
- Bleeding: Plavix increases risk of bleeding. Discontinue 5 days prior to elective surgery. (5.2)
- Discontinuation of Plavix: Premature discontinuation increases risk of cardiovascular events. (5.3)
- Recent transient ischemic attack or stroke: Combination use of Plavix and aspirin in these patients was not shown to be more effective than Plavix alone, but was shown to increase major bleeding. (5.4)
- Thrombotic thrombocytopenic purpura (TTP): TTP has been reported with Plavix, including fatal cases. (5.5)
2.3 CYP2C19 Poor Metabolizers

CYP2C19 poor metabolizer status is associated with diminished antiplatelet response to clopidogrel. Although a higher dose regimen (600 mg loading dose followed by 150 mg once daily) in poor metabolizers increases antiplatelet response [see Clinical Pharmacology (12.5)], an appropriate dose regimen for this patient population has not been established in clinical outcome trials.

5.1 Diminished Antiplatelet Activity Due to Impaired CYP2C19 Function

Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is entirely due to an active metabolite. The metabolism of clopidogrel to its active metabolite can be impaired by genetic variations in CYP2C19 [see Boxed Warning] and by concomitant medications that interfere with CYP2C19. Avoid concomitant use of Plavix and drugs that inhibit CYP2C19 activity. Co-administration of Plavix with omeprazole, a proton pump inhibitor that is an inhibitor of CYP2C19, reduces the pharmacological activity of Plavix if given concomitantly or if given 12 hours apart [see Drug Interactions (7.1)].

7.1 CYP2C19 Inhibitors

Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of drugs that inhibit the activity of this enzyme results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition. Avoid concomitant use of drugs that inhibit CYP2C19, e.g., omeprazole [see Warnings and Precautions (5.1) and Clinical Pharmacology (12.5)].

Omeprazole

In a crossover clinical study, 72 healthy subjects were administered Plavix (300 mg loading dose followed by 75 mg per day) alone and with omeprazole (80 mg at the same time as Plavix) for 5 days. The exposure to the active metabolite of clopidogrel was decreased by 46% (Day 1) and 42% (Day 5) when Plavix and omeprazole were administered together. Mean inhibition of platelet aggregation was diminished by 47% (24 hours) and 30% (Day 5) when Plavix and omeprazole were administered together.

In another study, 72 healthy subjects were given the same doses of Plavix and omeprazole but the drugs were administered 12 hours apart; the results were similar, indicating that administering Plavix and omeprazole at different times does not prevent their interaction [see Warnings and Precautions (5.1)].

12.5 Pharmacogenomics

CYP2C19 is involved in the formation of both the active metabolite and the 2-oxo-clopidogrel intermediate metabolite. Clopidogrel active metabolite pharmacokinetics and antiplatelet effects, as measured by ex vivo platelet aggregation assays, differ according to CYP2C19 genotype. Genetic variants of other CYP450 enzymes may also affect the formation of clopidogrel’s active metabolite.

The CYP2C19*1 allele corresponds to fully functional metabolism while the CYP2C19*2 and *3 alleles are nonfunctional. CYP2C19*2 and *3 account for the majority of reduced function alleles in white (85%) and Asian (99%) poor metabolizers. Other alleles associated with absent or reduced metabolism are less frequent, and include, but are not limited to, CYP2C19*4, *5, *6, *7, and *8. A patient with poor metabolizer status will possess two loss-of-function alleles as defined above. Published frequencies for poor CYP2C19 metabolizer genotypes are approximately 2% for whites, 4% for blacks and 14% for Chinese. Tests are available to determine a patient’s CYP2C19 genotype.

A crossover study in 40 healthy subjects, 10 each in the four CYP2C19 metabolizer groups, evaluated pharmacokinetic and antiplatelet responses using 300 mg followed by 75 mg per day and 600 mg followed by 150 mg per day, each for a total of 5 days. Decreased active metabolite exposure and diminished inhibition of platelet aggregation were observed in the poor metabolizers as compared to the other groups. When poor metabolizers received the 600 mg/150 mg regimen, active metabolite exposure and antiplatelet response were greater than with the 300 mg/75 mg regimen (see Table 3). An appropriate dose regimen for this patient population has not been established in clinical outcome trials.
Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C19 Genotype and Clopidogrel Therapy: 2013 Update

SA Scott¹, K Sangkuhl², CM Stein³, J-S Hulot⁴,⁵, JL Mega⁶, DM Roden⁷, TE Klein², MS Sabatine⁶, JA Johnson⁸,⁹,¹⁰ and AR Shuldiner¹¹,¹²
**Plavix (Clopidogrel) and CYP2C19 CPIC Guidelines**

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

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

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

\(^a\)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.
Plavix (Clopidogrel) and CYP2C19 CPIC Guidelines

Figure 1  Algorithm for suggested clinical actions based on CYP2C19 genotype when considering treatment with clopidogrel for ACS patients undergoing PCI (ACS/PCI). 1Other rare CYP2C19 genotypes exist beyond those illustrated (see Supplementary Materials and Methods online for other genotypes and frequencies). 2Note that prasugrel and ticagrelor are recommended only when not contraindicated clinically. ACS, acute coronary syndrome; EM, extensive metabolizer; IM, intermediate metabolizer; PCI, percutaneous coronary intervention; PM, poor metabolizer; UM, ultrarapid metabolizer.
Figure 1. Sample Epic Best Practice Advisory alert for clopidogrel-CYP2C19 implementation. BPA alerts are presented to the ordering physician in the EHR when a clopidogrel order is linked with an actionable CYP2C19 genotype. Physicians are provided email and phone contacts for additional help and a weblink to the Pharmacogenomics Knowledgebase (http://www.pharmgkb.org/) for additional information. PCI, percutaneous coronary intervention; PMP, Personalized Medicine Program.
### TABLE II. CYP2C19 Test Ordering and Adoption

<table>
<thead>
<tr>
<th>Implementation metric</th>
<th>No. of patients (%)</th>
<th>P-Value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients undergoing left heart catheterization and/or a PCI (preemptive genotyping)</td>
<td>1,479</td>
<td></td>
</tr>
<tr>
<td>Number of patients receiving CYP2C19 test in year 1</td>
<td>1,097</td>
<td></td>
</tr>
<tr>
<td>Number of tests successfully processed in lab</td>
<td>1,097</td>
<td></td>
</tr>
<tr>
<td>Year 1 test adoption rate</td>
<td>1,097/1,479 (74)</td>
<td></td>
</tr>
<tr>
<td>First 2 months (July and August 2012)</td>
<td>113/239 (47)</td>
<td></td>
</tr>
<tr>
<td>Last 2 months (May and June 2013)</td>
<td>208/252 (83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCI patients only</td>
<td>291</td>
<td></td>
</tr>
<tr>
<td>Number of patients receiving CYP2C19 test in year 1</td>
<td>247</td>
<td></td>
</tr>
<tr>
<td>Number of tests successfully processed in lab</td>
<td>247</td>
<td></td>
</tr>
<tr>
<td>Year 1 test adoption rate</td>
<td>247/291 (84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>First 2 months (June and July 2012)</td>
<td>30/48 (63)</td>
<td></td>
</tr>
<tr>
<td>Last 2 months (May and June 2012)</td>
<td>40/41 (98)</td>
<td></td>
</tr>
</tbody>
</table>

PCI, percutaneous coronary intervention.

<sup>a</sup>P-Values provided for CYP2C19 test adoption rates between first 2 months of implementation and last 2 months of implementation.
## TABLE III. CYP2C19 Pharmacogenetic Test Results and Classification

<table>
<thead>
<tr>
<th>Phenotype (metabolism status)</th>
<th>No. of patients (%) n = 1,097</th>
<th>Diplotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extensive metabolizer (normal)</td>
<td>422 (38.5)</td>
<td>*1/*1</td>
</tr>
<tr>
<td></td>
<td>287 (26.1)</td>
<td></td>
</tr>
<tr>
<td>Intermediate metabolizer (impaired)</td>
<td>218 (19.9)</td>
<td>*1/*2</td>
</tr>
<tr>
<td></td>
<td>61 (5.6)</td>
<td>*2/*17</td>
</tr>
<tr>
<td></td>
<td>3 (0.3)</td>
<td>*1/*8</td>
</tr>
<tr>
<td></td>
<td>1 (0.1)</td>
<td>*4/*17</td>
</tr>
<tr>
<td></td>
<td>1 (0.1)</td>
<td>*8/*17</td>
</tr>
<tr>
<td></td>
<td>1 (0.1)</td>
<td>*1/*3</td>
</tr>
<tr>
<td></td>
<td>1 (0.1)</td>
<td>*1/*4</td>
</tr>
<tr>
<td></td>
<td>1 (0.1)</td>
<td>*1/*6</td>
</tr>
<tr>
<td>Poor metabolizer (very impaired)</td>
<td>19 (1.7)</td>
<td>*1/*5, *3/*17, *5/*17, 6/*17</td>
</tr>
<tr>
<td></td>
<td>17 (1.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 (0.2)</td>
<td>*2/*2</td>
</tr>
<tr>
<td></td>
<td>None detected</td>
<td>*2/*4, *2/*5, *2/*6, *2/*8, *3/*3, *3/*4, *3/*5, *3/*6,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*6/*6, *6/*8, *8/*8</td>
</tr>
<tr>
<td>Ultrapid metabolizer (enhanced)</td>
<td>361 (32.9)</td>
<td>*1/*17</td>
</tr>
<tr>
<td></td>
<td>303(27.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>58 (5.3)</td>
<td>*17/*17</td>
</tr>
<tr>
<td>Unknown (uncharacterized)</td>
<td>8 (0.8)</td>
<td>*1/*10</td>
</tr>
<tr>
<td></td>
<td>2 (0.2)</td>
<td>*2/*10</td>
</tr>
<tr>
<td></td>
<td>1 (0.1)</td>
<td>*1/*9</td>
</tr>
<tr>
<td></td>
<td>1 (0.1)</td>
<td>*13/*17</td>
</tr>
<tr>
<td></td>
<td>1 (0.1)</td>
<td>*4/*17/*17</td>
</tr>
</tbody>
</table>
Figure 3. Clinical metrics in PCI patients with actionable genotypes. PCI, percutaneous coronary intervention; 3x, three times; diplotype classifications for intermediate and poor metabolizers provided in Table I.
PGx Implementation Summary

• There are many academic, private, and public healthcare systems that have successfully implemented clinical PGx services into their respective systems

• The results of clinical PGx implementation efforts have been largely positive with benefits to patient outcomes
Summary and Conclusions
PGx Biomarkers are Improving the Efficiency of Pharmacotherapy

Current approach
Drug prescribed

Prescription filled empiric dose

Prescriber remembers that genetic variants modulate the actions of the prescribed drug

Genetic test ordered; results interpreted

Patient recontacted with result and advised to change drug or dose

Future approach
Genotype data preemptively acquired and deposited into the Electronic Medical Record

Drug prescribed

Point of care order entry system accesses genotype on file; suggests drug/dose adjustment

Prescription filled genotype-guided dose

Pharmacogenomics: The Genetics of Variable Drug Responses
Dan M. Roden, Russell A. Wilke, Heyo K. Kroemer and C. Michael Stein
Circulation 2011;123;1661-1670
Summary and Conclusions

• Currently there are 166 PGx recommendations in the FDA approved package inserts of prescription drugs.

• Pharmacists are the most prepared clinicians for interpreting the recommendations and for counseling patients.

• The flow of PGx information into clinical practice will significantly increase in the near future and we must be prepared for it.
Summary and Conclusions

• PGx approaches to pharmacotherapy are cost effective and will contribute to decreases in health care expenditures and suboptimal outcomes
Summary and Conclusions
Bonus Material:
PGx Informed Drug Discovery
Learning from exceptional drug responders

The US National Cancer Institute is launching an ‘exceptional responder’ programme to see whether outliers from failed cancer trials can open up new drug development avenues.
Translational Drug Discovery: PCSK9 As A Druggable Target

Single-minded: Helen Hobbs and Jonathan Cohen’s approach to heart-disease genetics yielded a target for drugs that could compete with statins.
When Sharlayne Tracy showed up at the clinical suite in the University of Texas (UT) Southwestern Medical Center in Dallas last January, the bandage wrapped around her left wrist was the only sign of anything medically amiss. The bandage covered a minor injury from a cheerleading practice led by Tracy, a 40-year-old African American who is an aerobics instructor, a mother of two and a college student pursuing a degree in business. "I feel like I'm healthy as a horse," she said.

Indeed, Tracy’s well-being has been inspiring to doctors, geneticists and now pharmaceutical companies precisely because she is so normal. Using every tool in the modern diagnostic arsenal — from brain scans and kidney sonograms to 24-hour blood-pressure monitors and cognitive tests — researchers at the Texas medical centre have diagnostically sliced and diced Tracy to make sure that the two highly unusual genetic mutations she has carried for her entire life have produced nothing more startling than an incredibly low level of cholesterol in her blood. At a time when the target for low-density lipoprotein (LDL) cholesterol, more commonly called ‘bad cholesterol’, in Americans’ blood is less than 100 milligrams per decilitre (a level many people fail to achieve), Tracy’s level is just 14.
Translational Drug Discovery: 
PCSK9 As A Druggable Target

Figure 2. Schematic representation of the intracellular and extracellular pathways of proprotein convertase subtilisin kexin 9 (PCSK9) induced degradation of the low-density lipoprotein receptor (LDLR). When PCSK9 levels are high or if it has a gain-of-function, it will enhance the degradation of the LDLR using both the intracellular and the extracellular pathways leading to the degradation of the (PCSK9=LDLR) complex in lysosomes. This results in low levels of the LDLR at the cell surface and increased levels of circulating LDL-C. In absence or under low levels of PCSK9, cell surface LDLR levels are high and the LDLR can be recycled back to the surface after delivery of LDL particles to acidic endosomes. The evidence for the intracellular pathway is based on the knockdown of clathrin light chains in the human hepatocellular carcinoma HepG2 cells. The extracellular pathway-specific treatments include the use of a monoclonal antibody (mAb), an inhibiting adenectin or a small-molecule epidermal growth factor-A (EGF-A)–like inhibitor. TGN indicates Trans Golgi Network.

Circ Res. 2014;114:1022-1036
doi: 10.1161/CIRCRESAHA.114.301621
Sequence Variations in PCSK9, Low LDL, and Protection against Coronary Heart Disease

Jonathan C. Cohen, Ph.D., Eric Boerwinkle, Ph.D., Thomas H. Mosley, Jr., Ph.D., and Helen H. Hobbs, M.D.
Atorvastatin with or without an Antibody to PCSK9 in Primary Hypercholesterolemia

Eli M. Roth, M.D., James M. McKenney, Pharm.D., Corinne Hanotin, M.D., Gaelle Asset, M.Sc., and Evan A. Stein, M.D., Ph.D.
Translational Drug Discovery: 
PCSK9 As A Druggable Target

Figure 1. Mean Percent Change from Baseline in Low-Density Lipoprotein (LDL) Cholesterol Levels, According to Treatment Group.

Shown are the results for the primary efficacy outcome: the mean percent change from baseline in LDL cholesterol levels to week 8, as calculated with the use of the last-observation-carried-forward (LOCF) method. Results are also shown for the entire double-blind treatment phase (week 0 to week 8) and the follow-up period (week 8 to week 16). All analyses were performed in the modified intention-to-treat population, which included all patients who underwent randomization and who had a primary end point that could be evaluated. The P value was calculated with the use of an analysis of covariance including terms for treatment and baseline value. I bars indicate standard errors.
A 52-Week Placebo-Controlled Trial of Evolocumab in Hyperlipidemia

Dirk J. Blom, M.D., Ph.D., Tomas Hala, M.D., Michael Bolognese, M.D., Michael J. Lillestol, M.D., Phillip D. Toth, M.D., Lesley Burgess, M.B., B.Ch., M.Med., Ph.D., Richard Ceska, M.D., Ph.D., Eli Roth, M.D., Michael J. Koren, M.D., Christie M. Ballantyne, M.D., Maria Laura Monsalvo, M.D., Kate Tsirtsonis, M.Sc., Jae B. Kim, M.D., Rob Scott, M.D., Scott M. Wasserman, M.D., and Evan A. Stein, M.D., Ph.D., for the DESCARTES Investigators*
# Translational Drug Discovery: PCSK9 As A Druggable Target

## Table 2. Low-Density Lipoprotein (LDL) Cholesterol Levels at Baseline and at Week 52, According to Background Lipid-Lowering Therapy before Randomization.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Diet Alone</th>
<th>Diet plus 10 mg of Atorvastatin</th>
<th>Diet plus 80 mg of Atorvastatin</th>
<th>Diet plus 80 mg of Atorvastatin plus 10 mg of Ezetimibe</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (±SD) LDL cholesterol at baseline — mg/dl</td>
<td>Placebo (N = 37)</td>
<td>Evolocumab (N = 74)</td>
<td>Placebo (N = 129)</td>
<td>Evolocumab (N = 254)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>112.3±15.9</td>
<td>111.6±15.2</td>
<td>98.4±14.5</td>
<td>101.3±15.1</td>
<td></td>
</tr>
<tr>
<td>No. of patients evaluated at week 52†</td>
<td>31</td>
<td>67</td>
<td>113</td>
<td>233</td>
<td></td>
</tr>
<tr>
<td>Least-squares mean (±SE) percent change from baseline in LDL cholesterol at week 52</td>
<td>4.2±3.5</td>
<td>−51.5±2.4</td>
<td>6.9±2.2</td>
<td>−54.7±1.5</td>
<td></td>
</tr>
<tr>
<td>Least-squares mean (±SE) percent change from baseline in LDL cholesterol vs. placebo at week 52</td>
<td>−55.7±4.2</td>
<td>−61.6±2.6</td>
<td>−56.8±5.3</td>
<td>−48.5±5.2</td>
<td>−57.0±2.1</td>
</tr>
<tr>
<td>Mean (±SE) LDL cholesterol at week 52 — mg/dl</td>
<td>Placebo (N = 63)</td>
<td>Evolocumab (N = 126)</td>
<td>Placebo (N = 73)</td>
<td>Evolocumab (N = 145)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>119.8±32.4</td>
<td>116.8±35.3</td>
<td>94.6±12.9</td>
<td>96.2±13.3</td>
<td></td>
</tr>
<tr>
<td>Patients with LDL cholesterol &lt;70 mg/dl at week 52 — no. (%)</td>
<td>1 (3.2)</td>
<td>56 (83.6)</td>
<td>6 (5.3)</td>
<td>210 (90.1)</td>
<td></td>
</tr>
</tbody>
</table>

* Cholesterol was measured by means of ultracentrifugation. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.
† Included are patients within each background therapy in whom LDL cholesterol was measured at baseline and at week 52.
Translational Drug Discovery: 
PCSK9 As A Druggable Target

Figure 2. Percent Reduction from Baseline in Low-Density Lipoprotein (LDL) Cholesterol Levels in the Evolocumab Group, as Compared with the Placebo Group, at Weeks 12 and 52, According to Background Lipid-Lowering Therapy.

Values are means with lower 95% confidence limits (as indicated by T bars) in the active-treatment groups after taking into account the values in the placebo group. LDL cholesterol was measured by means of ultracentrifugation separation.
Anti-PCSK9 Antibody Effectively Lowers Cholesterol in Patients With Statin Intolerance

The GAUSS-2 Randomized, Placebo-Controlled Phase 3 Clinical Trial of Evolocumab

Erik Stroes, MD, PhD,* David Colquhoun, MD,† David Sullivan, MD,‡ Fernando Civeira, MD,§
Robert S. Rosenson, MD,|| Gerald F. Watts, DSc, PhD, DM,¶ Eric Bruckert, MD,# Leslie Cho, MD,**
Ricardo Dent, MD,†† Beat Knusel, PhD,†† Allen Xue, PhD,†† Rob Scott, MD,††
Scott M. Wasserman, MD,†† Michael Rocco, MD,¶¶ for the GAUSS-2 Investigators

*Amsterdam, the Netherlands; Auchenflower, Camperdown, and Perth, Australia; Zargoza, Spain;
New York, New York; Paris, France; Cleveland, Ohio; and Thousand Oaks, California
Amgen Says FDA Accepts BLA For Cholesterol Drug Evolocumab

By RTT News, November 10, 2014, 09:32:00 AM EDT

(RTTNews.com) - Amgen Inc. (AMGN) Monday said the U.S. Food and Drug Administration has accepted for review the drugmaker's Biologics License Application for cholesterol-lowering medication, evolocumab.

The FDA has set August 27, 2015 as the Prescription Drug User Fee Act date for the application.

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Summary and Conclusions

• PGx informed translational drug discovery efforts are far more efficient than traditional approaches that have contributed to the current R&D success rates

• PGx informed translational approaches offer the promise of improved outcomes for many individuals that are afflicted with chronic/acquired disorders