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PharmGenEd™: Bridging the Gap Between Science & Practice

Train-the-Trainer Session for Cardiology I: Warfarin and Statins
Tuesday, September 21, 2010

Train-the-Trainer Agenda

1. Introduction
   - Objective of PharmGenEd™ program
   - Shared curriculum and format
   - Introduction of author
2. Review of educational content for selected therapeutic area
3. Future webinar dates
   - Program implementation
   - Other therapeutic areas
4. Contact information
5. Survey instruments
   - Post training survey for trainers
6. Question & Answer (Q & A) session

Disclaimer

This presentation was supported by Grant Number IU38GD000070 from Centers for Disease Control and Prevention (CDC). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of CDC.

The content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should seek the advice of their physicians, pharmacists, or other qualified health providers with any questions they may have regarding a medical condition or a medication.
Overall Objective of PharmGenEd™ Program

- The "Pharmacogenomics Education Program: Bridging the Gap between Science and Practice" (PharmGenEd™) is an evidence-based pharmacogenomics education program designed for pharmacists and physicians, pharmacy and medical students, and other healthcare professionals.

- The overall objective of the PharmGenEd™ program is to increase awareness about current knowledge of the validity and utility of pharmacogenomic tests and the potential implications of benefits and harms from use of the tests.

Shared Curriculum

- Educational Materials (each 1 hour)
  - Asthma
  - Cardiology I (warfarin & statins)
  - Cardiology II (clopidogrel & beta blockers)
  - Concepts and clinical applications
  - Economic issues
  - Oncology I (solid tumors)
  - Oncology II (hematologic malignancies)
  - Psychiatry I (depression)
  - Psychiatry II (antipsychotics)

- Future webinar dates for these sessions will be provided later

Therapeutic Area Discussion

- Format
  - Patient case
  - Gene/Allele of interest
  - Functional effect
  - Population prevalence
  - Clinical relevance (dosing/selection, efficacy, and toxicity)
  - Genomic test and testing recommendation
  - Patient case summary

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University of Illinois at Chicago
Learning Objectives

- Upon completion of this program, participants will be able to:
  - Identify specific drug therapies used in cardiology in which pharmacogenomic testing can be applied in the clinical setting
  - Summarize evidence-based recommendations for pharmacogenomic testing
  - Using patient case scenarios, formulate a plan for pharmacogenomics testing based upon available scientific evidence

Outline

- Warfarin pharmacogenomics
  - Background
  - CYP2C9
  - VKORC1
  - CYP4F2
  - Clinical applications
- Statin pharmacogenomics
  - Background
  - SLCO1B1
  - KIF6
  - Clinical applications

Patient Case

- JJ is a 71 year-old non-Hispanic Caucasian woman who starts on warfarin for new onset atrial fibrillation (target INR of 2.5)
  - PMH is significant for hypertension and hyperlipidemia.
  - SH: she does not smoke or drink alcohol.
  - No liver disease
  - Current medications: diltiazem XL 180 mg PO daily and lisinopril 10 mg PO daily
  - Vitals: 5'4" and 150 lbs
  - Her baseline INR is 1.0
  - Genotypes: CYP2C9*3/*3 and VKORC1 -1639A/A

- Question: What dose of warfarin is appropriate to start for JJ?

Grice et al 2008
### Warfarin: Background

- Most widely prescribed oral anticoagulant
- High incidence of adverse events
  - Among the top 10 drugs with the largest number of serious adverse events reports in FDA’s Adverse Event Reporting System
  - Associated with about 29,000 emergency room visits per year for bleeding complications
- High inter-individual variability (~16 fold) in its dose requirements

Wysowski et al. 2007

Higashi et al. 2002

### Warfarin: Factors Affecting Dose Variability

- Non-genetic factors
  - Age
  - Body size
  - Disease states (liver, thyroid, etc)
  - Vitamin K intake
- Genetic polymorphisms explain 30-40% of inter-individual variability in warfarin dose requirements in predominately Caucasian populations (Takeuchi et al. 2009, Gage et al. 2008).
  - CYP2C9 (5-15%)
  - VKORC1 (10-30%)
  - CYP4F2 (1-2%)


### Pharmacology of Warfarin

- CYP1A2, CYP2C19
- CYP3A
- CYP2C9
- CYP3A4

- R-warfarin
- S-warfarin

- Vitamin K epoxide reductase

- Vitamin K epoxide reductase

- γ-glutamyl carboxylase

- Precursors of clotting factors (II, VII, IX, X)

- Activated clotting factors (II, VII, IX, X)

### Warfarin: CYP2C9

- **Gene/Alleles:** CYP2C9*2, CYP2C9*3
  - Two common non-synonymous single nucleotide polymorphisms (SNPs)

- **Functional Effect:**

<table>
<thead>
<tr>
<th>Allele</th>
<th>NT change</th>
<th>AA change</th>
<th>Enzyme activity (%)</th>
<th>a</th>
</tr>
</thead>
<tbody>
<tr>
<td>*2</td>
<td>rs1799853;C&gt;T</td>
<td>Arg144Cys</td>
<td>60-70%</td>
<td>percent of normal enzyme activity</td>
</tr>
<tr>
<td>*3</td>
<td>rs1057910; A&gt;C</td>
<td>Ile359Leu</td>
<td>5%</td>
<td>NT: nucleotide, AA: amino acid</td>
</tr>
</tbody>
</table>


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**Warfarin: CYP2C9**

- Population Prevalence (%):

<table>
<thead>
<tr>
<th>Allele</th>
<th>Caucasian</th>
<th>African-American</th>
<th>Asian</th>
</tr>
</thead>
<tbody>
<tr>
<td>*2</td>
<td>19</td>
<td>2-8</td>
<td>0</td>
</tr>
<tr>
<td>*3</td>
<td>12</td>
<td>2-4</td>
<td>6-8</td>
</tr>
</tbody>
</table>

- CYP2C9*5, *6, *8, and *11 predominantly occur in individuals of African descent. Their allele frequencies range from 1 to 6% in African Americans. They have been associated with lower warfarin dose requirements in African Americans (Cavallari et al 2010).


---

**Warfarin: CYP2C9**

- Clinical Relevance: Dosing/Selection

<table>
<thead>
<tr>
<th>CYP2C9 Genotype</th>
<th>n=127</th>
<th>n=28</th>
<th>n=4</th>
<th>n=18</th>
<th>n=3</th>
<th>n=5</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1/*1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*1/*2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*1/*3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*2/*2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*2/*3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*3/*3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n=185 Caucasians

p=0.001

--

**Warfarin Gene/Allele: VKORC1**

- Gene/Alleles: VKORC1
  - VKORC1–1639 genotypes: GG, AG, AA
  - Haplotypes: A/B; five non-coding SNPs in linkage disequilibrium form two common haplotypes (A and B)

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>-4931 (rs7196616)</th>
<th>-1639 (rs9923231)</th>
<th>1173 (rs9934438)</th>
<th>1542 (rs8050894)</th>
<th>2255 (rs2359612)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>T</td>
<td>T</td>
<td>T</td>
<td>T</td>
<td>T</td>
<td>T</td>
</tr>
<tr>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>T</td>
<td>T</td>
<td>T</td>
<td>T</td>
<td>T</td>
<td>T</td>
</tr>
<tr>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
</tbody>
</table>


---

**Warfarin: VKORC1**

- Functional effect:
  - VKORC1 mRNA expression by haplotype

![Warfarin: VKORC1](image)
**Warfarin: VKORC1**

- Population prevalence of haplotype A (%):

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>Caucasian</th>
<th>AA</th>
<th>Asian</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>60</td>
<td>26</td>
<td>99</td>
</tr>
</tbody>
</table>

AA: African Americans

Rieder et al 2005

**Warfarin: CYP2C9 and VKORC1**

- Clinical Relevance: Dosing/Selection

<table>
<thead>
<tr>
<th>CYP2C9 or VKORC1 Variants</th>
<th>n</th>
<th>Average Warfarin Maintenance Dose (mg/wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild Type</td>
<td>56</td>
<td>44.7</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>37.4</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>26.3</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>17.6</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>8</td>
</tr>
</tbody>
</table>

Anderson et al 2007

**Warfarin: CYP2C9, VKORC1**

- Clinical Relevance

- Efficacy: Time to first therapeutic INR
  - VKORC1 haplotype was associated with time to first therapeutic INR
  - CYP2C9 genotype was not associated

Schwarz UI, et al. NEJM 2008;358:999-1008. Copyright © [2008] Massachusetts Medical Society. All rights reserved.
Warfarin: CYP2C9, VKORC1

**Clinical Relevance**
- **Toxicity**: Time to first INR > 4
  - Both VKORC1 haplotype and CYP2C9 genotype were associated with time to first INR > 4

Schwarz UI, et al. NEJM 2008;358:999-1008. Copyright © [2008] Massachusetts Medical Society. All rights reserved.

Warfarin: CYP2C9 and VKORC1

**Clinical Relevance: Toxicity**
- Major bleeding (%)

Limdi et al 2008

Warfarin: CYP4F2

**Gene/Allele**: CYP4F2 rs2108622:G>A

**Functional Effect** (McDonald et al 2009):
- Enzyme activity (%)

<table>
<thead>
<tr>
<th>Allele</th>
<th>NT change</th>
<th>AA change</th>
<th>Enzyme activity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2108622</td>
<td>G&gt;A</td>
<td>Val to Met</td>
<td>↓ vitamin K1 oxidase activity</td>
</tr>
</tbody>
</table>

**Population Prevalence (%)**:

<table>
<thead>
<tr>
<th>Allele</th>
<th>Caucasians</th>
<th>African Americans</th>
<th>Asians</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2108622</td>
<td>40</td>
<td>0-10</td>
<td>50</td>
</tr>
</tbody>
</table>


Warfarin: CYP4F2

**Clinical Relevance: Dosing/Selection**
- Not commonly used in clinical care
- AA required a higher warfarin dose (1 mg/day) than GG (Caldwell et al 2008)

**Clinical Relevance: Efficacy**
- No literature related to the CYP4F2 polymorphism impacting drug efficacy.

**Clinical Relevance: Toxicity**
- No literature related to the CYP4F2 polymorphism impacting drug toxicity.
Warfarin Pharmacogenomic Tests

• 5 tests cleared as an *in vitro* diagnostic device
  – Genotypes for two loci in *CYP2C9* and one locus in *VKORC1*
  – *CYP4F2* test is not commercially available
  – Assay performance time < 6 hrs
  – Cost: $300-500

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Warfarin Testing Recommendations

• Pharmacogenomic information is included on the Coumadin® label:
  – “Identification of risk factors for bleeding and certain genetic variations in *CYP2C9* and *VKORC1* in a patient may increase the need for more frequent INR monitoring and the use of lower warfarin doses…”
  – “The lower initiation doses should be considered for patients with certain genetic variations in *CYP2C9* and *VKORC1* enzymes…”
  – Information on the *CYP4F2* polymorphism is not included in the label.

Coumadin® prescribing information, 2007
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Warfarin Pharmacogenomic Dosing

• FDA Recommendation (mg/day)

<table>
<thead>
<tr>
<th>VKORC1 -1639 Genotype</th>
<th>*1/*1</th>
<th>*1/*2</th>
<th>*1/*3</th>
<th>*2/*2</th>
<th>*2/*3</th>
<th>*3/*3</th>
</tr>
</thead>
<tbody>
<tr>
<td>GG</td>
<td>5-7</td>
<td>5-7</td>
<td>3-4</td>
<td>3-4</td>
<td>3-4</td>
<td>0.5-2</td>
</tr>
<tr>
<td>AG</td>
<td>5-7</td>
<td>3-4</td>
<td>3-4</td>
<td>3-4</td>
<td>0.5-2</td>
<td>0.5-2</td>
</tr>
<tr>
<td>AA</td>
<td>3-4</td>
<td>3-4</td>
<td>0.5-2</td>
<td>0.5-2</td>
<td>0.5-2</td>
<td>0.5-2</td>
</tr>
</tbody>
</table>

CYP2C9 Genotype

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Warfarin Dosing Algorithms

• Estimate a warfarin dose which maintains a therapeutic INR by using genetic and non-genetic variables

• Linear regression model (Gage 2008, Lenzini 2010)
  – Explanatory variables: genetic and non-genetic variables
    – Genetic: *CYP2C9* and *VKORC1*
    – Non-Genetic: body surface area, target INR, smoking status, history of DVT/PE, African American race, use of amiodarone
  – Dependent variable: stable warfarin daily dose
Warfarin Dosing Algorithms

- Accuracy of Algorithms: $R^2$ values
  - $R^2$ indicates variability in data explained by the regression model
  - Pharmacogenomic vs. clinical dosing algorithms

<table>
<thead>
<tr>
<th></th>
<th>Pharmacogenomic</th>
<th>Clinical</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R^2$ (SD)</td>
<td>54% (5%)</td>
<td>17% (4%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

- Pharmacogenomic algorithm comparing Caucasians with African-Americans

<table>
<thead>
<tr>
<th></th>
<th>Caucasians</th>
<th>African Americans</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R^2$</td>
<td>57%</td>
<td>31%</td>
</tr>
</tbody>
</table>


- Probability to correctly identify patients requiring low or high warfarin doses

- A publicly available warfarin dosing algorithm
- Based on data from over 1,000 patients (Gage et al 2008)
- May be used to adjust warfarin dose in patients whose genotype information is available before the 6th dose of warfarin
  - $R^2$ on day 5 is ~60%, meaning 60% of data variability is explained by the algorithm (Lenzini et al 2010).
**Patient Case Summary**

- **Non-genetic factors**
  - Age: 71
  - Caucasian
  - Indication: afib
  - Non smoker, non-drinker of EtOH
  - 5'4", 150 lbs
  - Normal liver function
  - Baseline INR=1.0
  - No significant drug interaction with warfarin
- Based on JJ’s non-genetic factors, JJ is likely to start on 5 mg of warfarin according to the ACC Chest Guideline (Ansell et al 2008)

**Patient Case Summary**

- JJ has CYP2C9*3/*3 and VKORC1-1639A/A
- According to the package insert, JJ’s estimated dose range is 0.5-2 mg/day
  - [www.warfarindosing.org](http://www.warfarindosing.org) estimates 2.9 mg mini loading dose and 1.3 mg/day of maintenance dose
- CYP2C9 variant carriers may be able to achieve steady state more quickly with a loading dose (Linder et al 2002)
- Given her CYP2C9*3/*3 and VCORKC1 A/A status, 1.5 mg/day warfarin is appropriate

**Warfarin Dosing Algorithms**

- Limitations of current warfarin pharmacogenomic dosing algorithms
  - Generalizability
    - African-Americans or others with rare indications
  - Not all variables were included as explanatory variables
  - Unpredictability of outliers from the regression line
    - Patients who require a high dose (≥ 7 mg/day)
- Careful monitoring, close follow up and sound clinical judgment are also important in warfarin dosing

**Warfarin Dosing Algorithms**

- Clinical Utility
  - Risk and benefit ratio of using a test in clinical practice (Flockhart et al 2008)
- Warfarin pharmacogenomic testing has not shown its clinical utility
  - A small study (Couma-Gen) showed no benefit of using the testing compared with no testing (Anderson et al 2007)
- Large multi-center trials are currently under way
Warfarin: Summary

- Genetic polymorphisms in *CYP2C9*, *VKORC1* and *CYP4F2* have been associated with inter-individual variability in warfarin dose requirements
  - *CYP2C9*: pharmacokinetics
  - *VKORC1* and *CYP4F2*: pharmacodynamics
- Pharmacogenomic warfarin dosing algorithms are an adjunct to sound clinical judgment

Patient Case

- DC is a 48 year-old African American male with a history of hypertension and type 2 diabetes
  - SH: Denies tobacco or alcohol use
  - FH: Brother developed statin-induced myopathy
  - Labs (fasting): LDL = 144 mg/dL, HDL = 30 mg/dL, and triglycerides = 175 mg/dL
  - Genotypes: *SLCO1B1* *1/*5 and *KIF6* 719Trp/Arg
- Question: Is DC a good candidate for statin therapy?
**Statins: Background**

- Among the most widely prescribed drugs
- Reduce the risk for cardiovascular events and death in both primary and secondary prevention of coronary heart disease (CHD)
- Recommended in patients with:
  - Elevated LDL
  - History of CHD or diabetes
  - CHD risk equivalent
  - 10-year CHD risk ≥20% 

**Statins Gene: SLCO1B1**

- Allele: SLCO1B1*5
- Functional Effect:
  - SLCO1B1 encodes for the organic anion transporting polypeptide C (OAT1B1)
  - OAT1B1 transports statins (except fluvastatin) to hepatocytes
  - SLCO1B1 *5
    - SNP (521T>C) nucleotide change results in amino acid change 174Val/Ala
    - Reduces OAT1B1 transport activity (Kameyama et al 2005)
    - Associated with increased statin concentrations thus increasing the risk for myopathy (Niemi et al 2006)

**Statin-Induced Myopathy**

- Defined as muscle pain or weakness with elevated creatinine kinase levels
- Symptoms range from mild myalgia to rhabdomyolysis
- Occurs at an incidence of 3 to 5% in clinical trials, but as high as 10% in clinical practice (Thompson PD et al 2003, Nichols GA et al 2007)
- Underlying mechanism is unknown, but risk factors include:
  - Higher statin doses
  - Use with drugs that increase statin bioavailability
  - Genetic variants affecting statin pharmacokinetics

**Statins: SLCO1B1*5**

- Population Prevalence: 
  - Allele frequency (%)
    - SLCO1B1 *5
      - Caucasian: 16
      - African-American: 1 to 2
      - Asian: 10 to 16

**Statins Gene: KIF6**

- **Allele:** 719Trp/Arg
- **Function Effect**
  - KIF6 encodes kinesin-like protein 6
  - Kinesin-like protein 6 is involved in transporting large molecules intra-cellularly along microtubules
  - KIF6 719Trp/Arg SNP associated with an increased risk of coronary events

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARE</td>
<td>Patients with CHD</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>Patients with CHD risk factors</td>
</tr>
<tr>
<td>WHS</td>
<td>Healthy women</td>
</tr>
<tr>
<td>PROVE IT-TIMI 22</td>
<td>Patients with ACS</td>
</tr>
</tbody>
</table>


**Statins: KIF6 719Trp/Arg**

- **Population Prevalence:**
  - **Allele frequency (%)**

<table>
<thead>
<tr>
<th>Allele</th>
<th>Caucasian</th>
<th>African-American</th>
<th>Asian</th>
</tr>
</thead>
<tbody>
<tr>
<td>719Arg</td>
<td>36</td>
<td>83</td>
<td>39 to 56</td>
</tr>
</tbody>
</table>


**Statins: Clinical Relevance**

- **Dosing/Selection**
  - PROVE IT-TIMI 22 study showed that KIF6 719Arg carriers benefit from high statin doses. (Iakoubova et al 2008)
    - Atorvastatin 80 mg/day reduced the risk for cardiovascular events by 41% compared to pravastatin 40 mg/day in Arg carriers
    - Trp allele homozygotes did not benefit from high-dose statin therapy
  - High-dose statins should be avoided in patients with the SLCO1B1*5 allele to reduce the potential risk for myopathy

**Statins: Clinical Relevance**

- **Efficacy**
  - CARE and WOSCOPS showed greater cardiac protection with pravastatin in KIF6 719Arg variant carriers versus non-carriers
  - Risk for CHD events with the 719Arg variant:

<table>
<thead>
<tr>
<th>Trial</th>
<th>Placebo arm</th>
<th>Statin arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARE</td>
<td>1.50 (1.05 to 2.15)</td>
<td>0.63 (0.46 to 0.86)*</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>1.55 (1.14 to 2.09)</td>
<td>0.50 (0.38 to 0.67)*</td>
</tr>
</tbody>
</table>

*Hazard ratio (95% CI) for CARE and odds ratio (95% CI) for WOSCOPS; Compared to placebo group with HR or OR set to 1 for the placebo group Iakoubova et al 2008
Statins: Toxicity

- *SLCO1B1*^*5* allele identified as a risk factor for statin-induced myopathy in a genome wide association study (GWAS) (Link et al 2008)
  - Included 85 subjects with simvastatin-induced myopathy
  - Odds ratio for myopathy:
    | Genotype | Odds ratio (95% CI) |
    |----------|---------------------|
    | TC       | 4.5 (2.6 to 7.7)    |
    | CC       | 16.9 (4.7 to 61.1)  |

- *5 allele also associated with less severe side effects leading to statin discontinuation* (Voora et al 2009)

Statins: Pharmacogenomic Test

- Pharmacogenomic Test(s)
  - Testing for the *SLCO1B1*^*5* and *KIF6* 719Trp/Arg genotypes are commercially available and costs about $500

- Testing Recommendation(s)
  - There are no recommendations regarding testing for the *SLCO1B1* or *KIF6* genotype

Patient Case Summary

- DC has the *SLCO1B1*^*5* allele associated with increased statin concentration
  - DC is at increased risk for statin-induced myopathy
  - High statin doses and drugs that increase statin bioavailability should be avoided
  - Fluvastatin may be considered if myopathy or intolerable myalgia develops

- DC has the *KIF6* allele associated with increased risk for cardiovascular events
  - DC is a good candidate for statin therapy to reduce the increased risk for CHD associated with the 719Arg allele

Statins: Summary

- Clinical utility of the testing has not been established

- *SLCO1B1* and *KIF6* are associated with inter-individual variability in statin pharmacokinetics and risk for adverse events
  - *SLCO1B1*^*5* increases the risk for statin-induced myopathy
  - genetic testing may be warranted in a patient with family history of statin-induced myopathy
  - *KIF6* testing may identify high risk patients who may need intensive statin therapy
Acknowledgements

- Author
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  - Larisa H. Cavallari, PharmD
  - Associate Professor
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- Reviewers and Editorial Staff
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  - Reviewers and Associate Editors
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References

FDA. Medical Devices. Available at: http://www.fda.gov/MedicalDevices/default.htm

Acknowledgements

- Author
  - Jaekyu Shin, PharmD, MS, BCPS
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The program is 100% funded by the CDC
(Grant Number IU38GD000070)

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