# Translational Initiatives in Pharmacogenomics at Mount Sinai

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Icahn School of Medicine at Mount Sinai
New York, NY

Mount Sinai


- 7 hospital campuses
- 1 leading medical school
- 36000 employees
- 45 non-surgical ambulatory care practices
- 6200 physicians including general practitioners and specialists
- More than 2000 residents and fellows
- 169,532 inpatient admissions
- Over 2,600,000 outpatient visits to offices and clinics (non-Emergency Department)
- 489,508 Emergency Department visits
- 3,535 beds
- 135 operating rooms
- 31 institutes

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# The Charles Bronfman Institute for Personalized Medicine

## BioMe™ Biobank

- Prospective collection of DNA and plasma samples linked to full EMR-based medical information for large-scale genomic medicine research
- DNA and plasma samples linkable with complete, de-identified electronic health record (Mount Sinai Data Warehouse)
- Allows associations to be discovered between genomics and clinical information (Therapeutic efficacy, ADR's, prevalent/incident disease, poor/good outcome)
- Written Informed consent
- Extended Family History Questionnaire
- Permission to re-contact participants for future research

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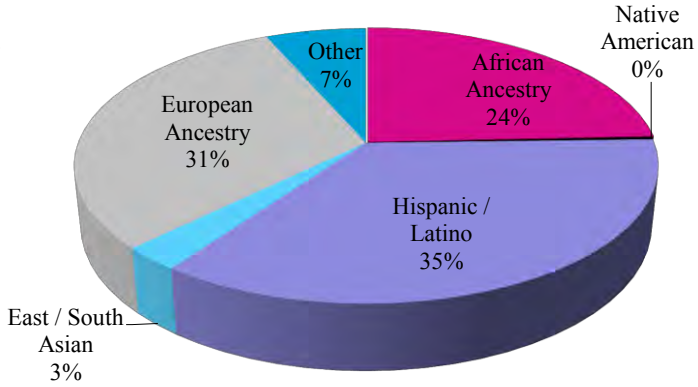
## BioMe™ Biobank Enrollment and Demographics

- > 32,000 patients enrolled
- ~ 500 new donors enroll per month

Female: 59%
Male: 41%

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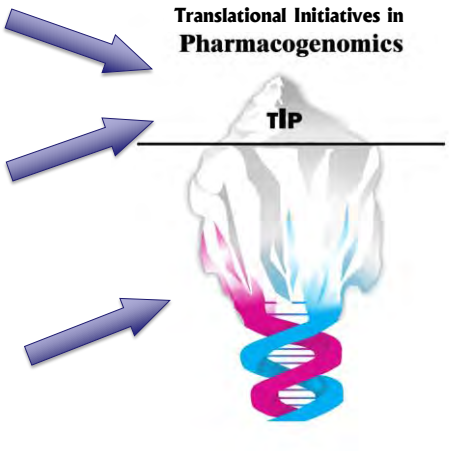
# Translational Initiatives in Pharmacogenomics

- Education
  - PGx elective rotation for residents and APPE students
  - MD training
  - Patient brochures
  - Student volunteer opportunities
  - Potential elective PGx course
- Personalized Healthcare
  - IPM PGx
  - eMERGE PGx
- Research
  - Expand the evidence base for drug-gene pairs
  - Develop and successfully implement best practices for PGx adoption into clinical care.

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# PGx Implementation Programs

## IPM PGx

- Main objective:
  - Develop process best-practices for implementation of Personalized Medicine
- Focus of research program
  - Providers

## eMERGE PGx

# PGx Implementation Programs

## IPM PGx

- 1000 Bio*Me* patients
- Internal Medicine Associates clinic
- Pre-emptive genotyping
  - Sequenom iPLEX ADME array
- Providers are consented and surveyed
- Unlimited number of drug-gene pairs
- CLIPMERGE
- EHR data collection

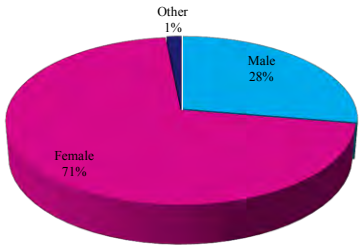
## eMERGE PGx

- 663 Bio*Me* and non-Bio*Me* patients
- Faculty Practice Associates clinic
- Pre-emptively sequenced
  - PGRNseq
- Providers are co-investigators
- CDS for simvastatin, clopidogrel and warfarin
- CLIPMERGE
- EHR data collection

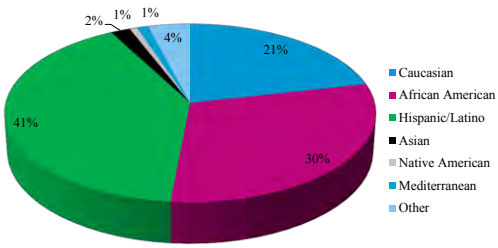
# Patient Demographics

N = 1641

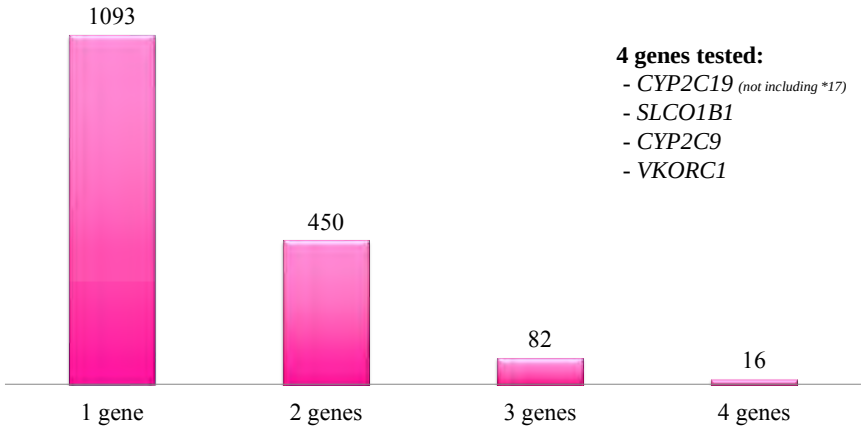
### Gender




### Race / Ethnicity



# 77% of patients have at least one actionable variant

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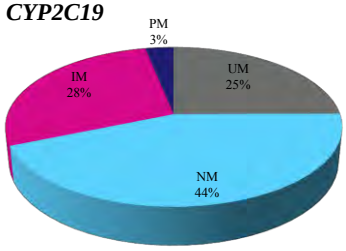
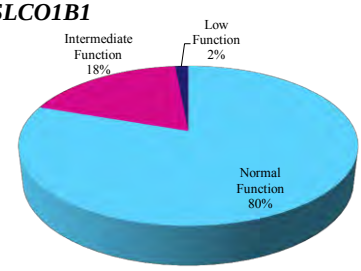
# Genotype Frequencies

N = 1641

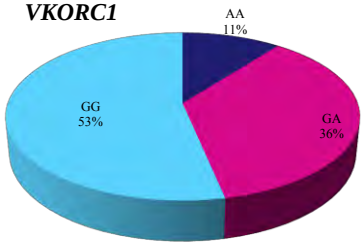
***CYP2C19***



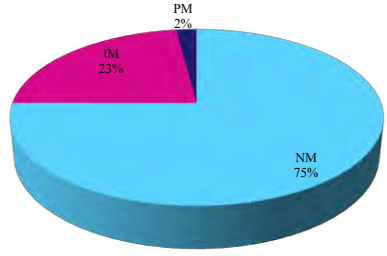

***SLCO1B1***




***VKORC1***




***CYP2C9***

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# Provider Training

- One hour training session
  - Video available online
- Complete a pre and post training questionnaire
- Have additional information on each drug-gene pair embedded in the CDS
- Post-CDS surveys



# Provider Survey Responses

I know enough about genetics and genomics to understand the test results.

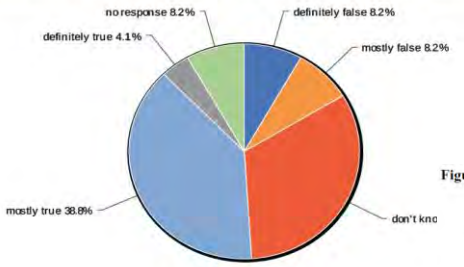
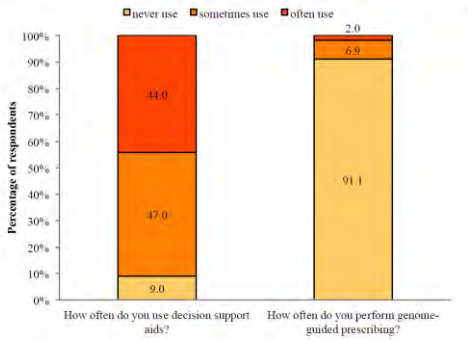



**Figure 2.** Experience with decision support aids and genome-guided prescribing.




Overby CL, et al. *J. Pers. Med.* **2014**, *4*, 35-49

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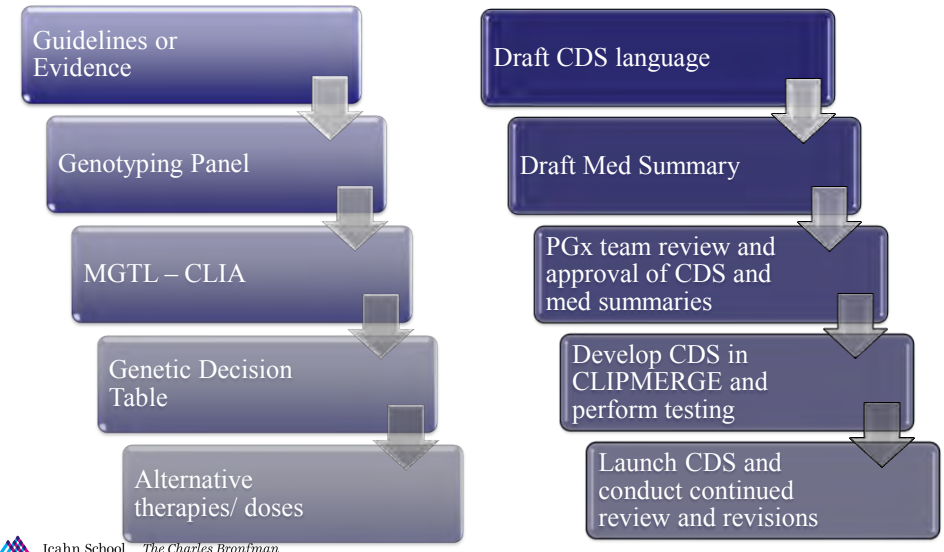
# PGx Clinical Implementation Process

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# What is CLIPMERGE?

- Advanced data management system that is external to, but communicates with Epic
- Clinical decision support engine
- Delivers guidance on actionable genomic variants in a manner that integrates with existing physician work processes
  - Real-time, point-of-care

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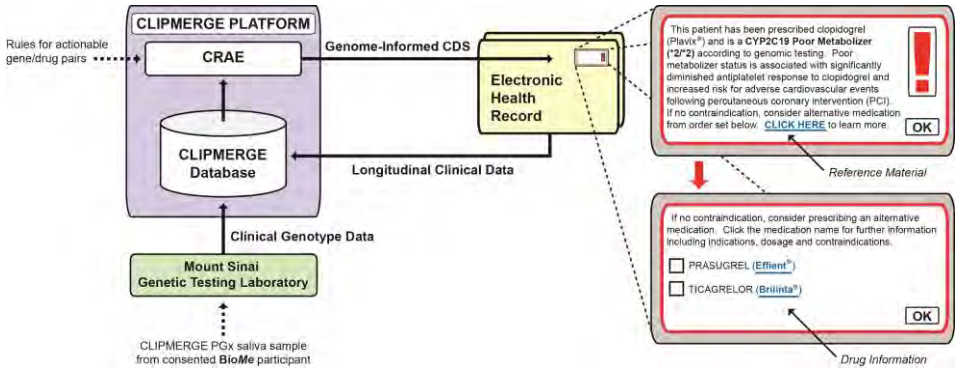
# CLIPMERGE

**C**linical **I**mplementation of **P**ersonalized **M**edicine through **E**lectronic Health **R**ecords and **Ge**nomics

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Gottesman et al. The CLIPMERGE PGx Program: Clinical Implementation of Personalized Medicine Through Electronic Health Records and Genomics-Pharmacogenomics. Clin Pharmacol Ther. 2013 Apr 3. doi: 10.1038/clpt.2013.72.

# Drug Gene Pairs

16

| Live | Under Development |
|---|---|
| ▸ Clopidogrel – *CYP2C19* | • Azathioprine – *TPMT* |
| ▸ Simvastatin – *SLCO1B1* | • Mercaptopurine – *TPMT* |
| ▸ Warfarin – *CYP2C9* | • Rasburicase – *G6PD* |
| ▸ Warfarin – *VKORC1* | • Dapsone – *G6PD* |
| ▸ Tramadol – *CYP2D6* | • Abacavir – *HLA-B*57:01* |
| ▸ Codeine – *CYP2D6* | • Carbamazepine – *HLA-B*15:02* |
| | • TCAs – *CYP2C19* |
| | • TCAs – *CYP2D6* |

# Warfarin *CYP2C9 / VKORC1* Example

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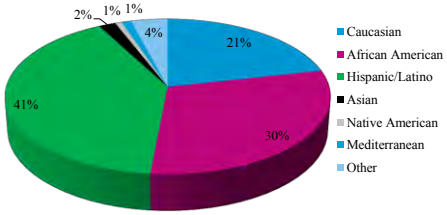
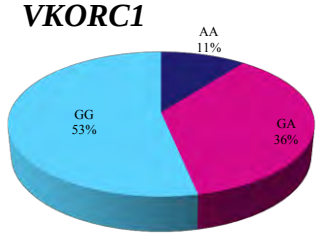
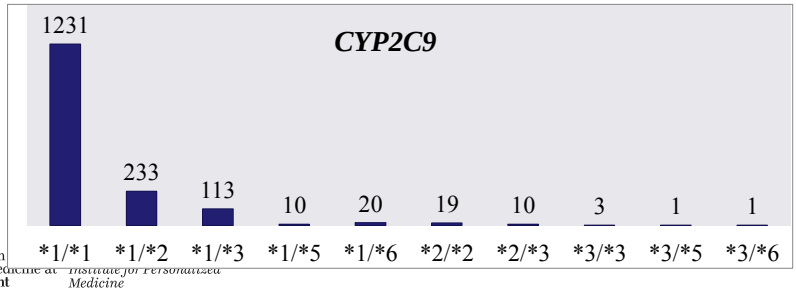
## PGx Patient Demographics

### Race / Ethnicity




### *VKORC1*

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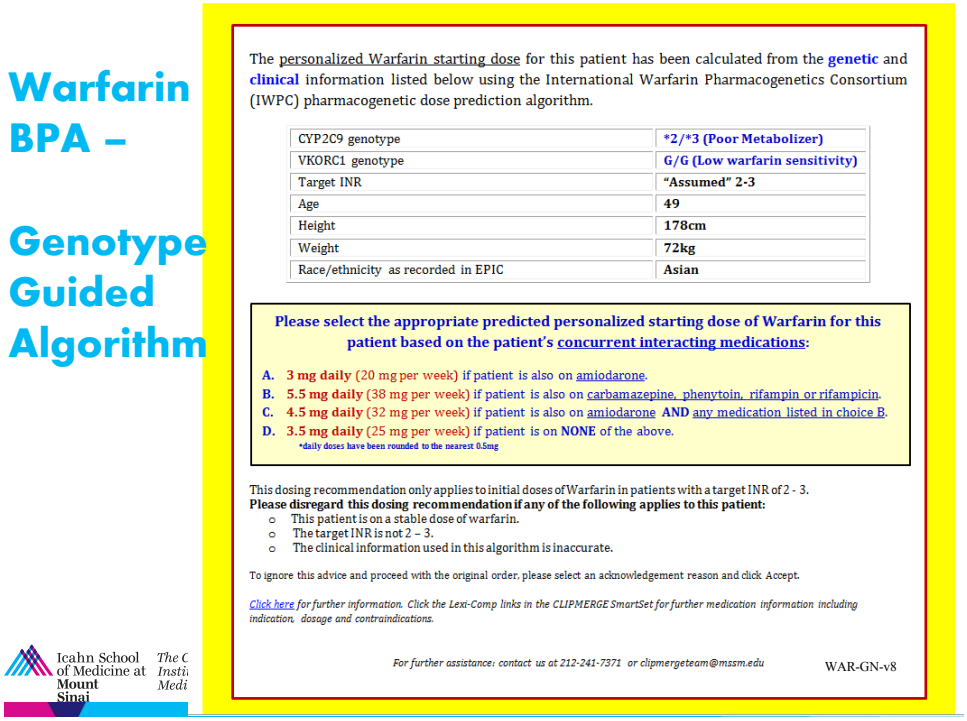
## Warfarin BPA – Genotype Guided Algorithm



The personalized Warfarin starting dose for this patient has been calculated from the **genetic** and **clinical** information listed below using the International Warfarin Pharmacogenetics Consortium (IWPC) pharmacogenetic dose prediction algorithm.

| | |
|---|---|
| CYP2C9 genotype | ***2/*3 (Poor Metabolizer)** |
| VKORC1 genotype | **G/G (Low warfarin sensitivity)** |
| Target INR | **"Assumed" 2-3** |
| Age | **49** |
| Height | **178cm** |
| Weight | **72kg** |
| Race/ethnicity as recorded in EPIC | **Asian** |

**Please select the appropriate predicted personalized starting dose of Warfarin for this patient based on the patient's concurrent interacting medications:**

A. **3 mg daily** (20 mg per week) if patient is also on amiodarone.
B. **5.5 mg daily** (38 mg per week) if patient is also on carbamazepine, phenytoin, rifampin or rifampicin.
C. **4.5 mg daily** (32 mg per week) if patient is also on amiodarone **AND** any medication listed in choice B.
D. **3.5 mg daily** (25 mg per week) if patient is on **NONE** of the above.

*daily doses have been rounded to the nearest 0.5mg

This dosing recommendation only applies to initial doses of Warfarin in patients with a target INR of 2 - 3.
**Please disregard this dosing recommendation if any of the following applies to this patient:**
- This patient is on a stable dose of warfarin.
- The target INR is not 2 – 3.
- The clinical information used in this algorithm is inaccurate.

To ignore this advice and proceed with the original order, please select an acknowledgement reason and click Accept.

*Click here for further information. Click the Lexi-Comp links in the CLIPMERGE SmartSet for further medication information including indication, dosage and contraindications.*

*For further assistance: contact us at 212-241-7371 or clipmergeteam@mssm.edu*

WAR-GN-v8

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## Simvastatin and *SLCO1B1* Example

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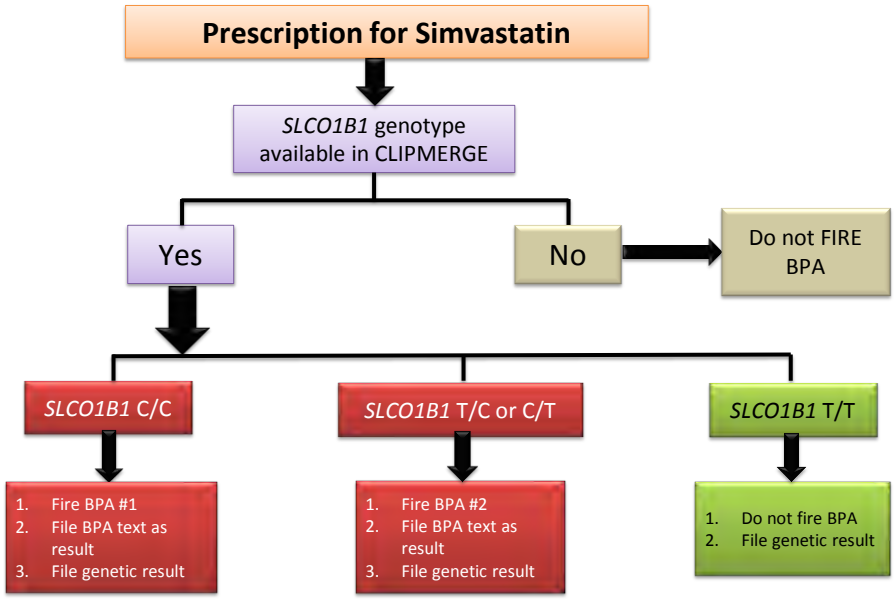





# Simvastatin BPA #1 – Poor Function

According to genetic testing, this patient has an ***SLCO1B1* C/C genotype at rs4149056.**
This genotype confers high myopathy risk with simvastatin, particularly with doses greater than 20mg.

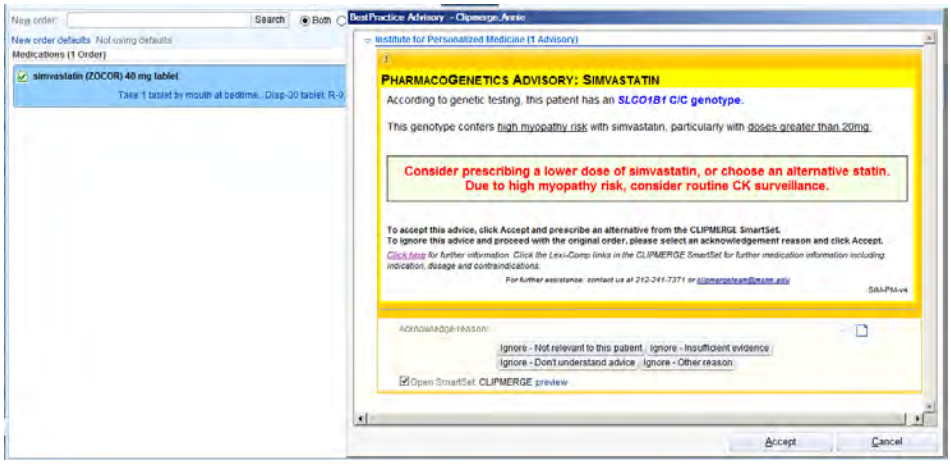
**Consider prescribing a lower dose of simvastatin, or choose an alternative statin.**
**Due to high myopathy risk, consider routine CK surveillance.**

**To accept this advice, click Accept and prescribe an alternative from the CLIPMERGE SmartSet.**
**To ignore this advice and proceed with the original order, select an Acknowledgement reason and click Accept.**

*Click here for further information. Click the Lexi-Comp links in the CLIPMERGE SmartSet for further medication information including indication, dosage and contraindications.*

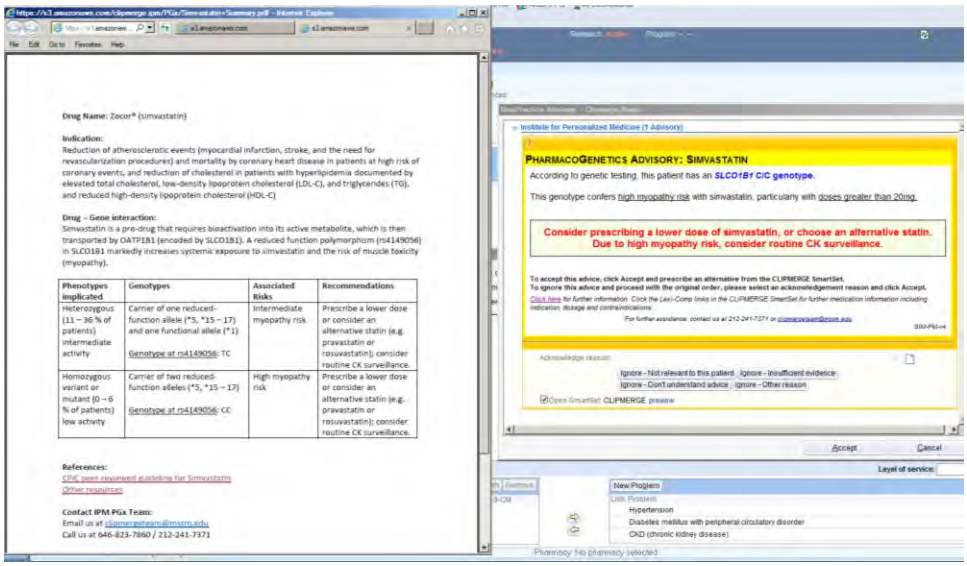
*For further assistance: contact us at 212-241-7371 or clipmergeteam@mssm.edu* SIM-PM-v4

# Simvastatin Alert in EMR

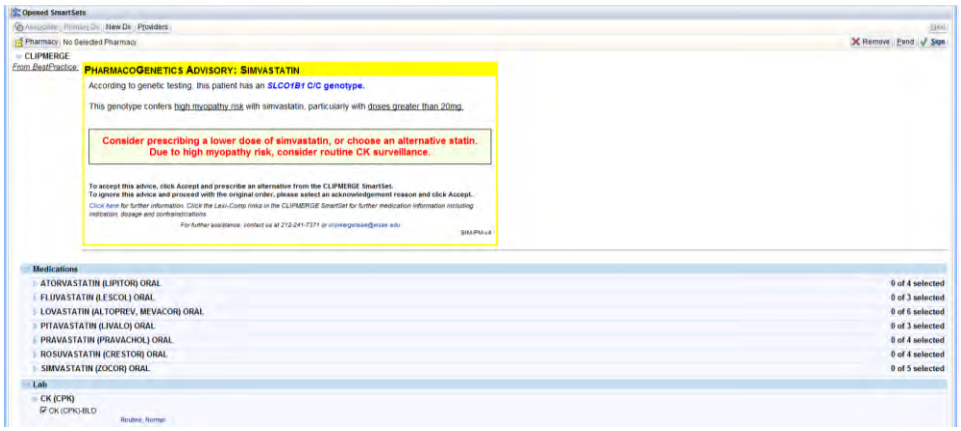





# Simvastatin Alert in EMR

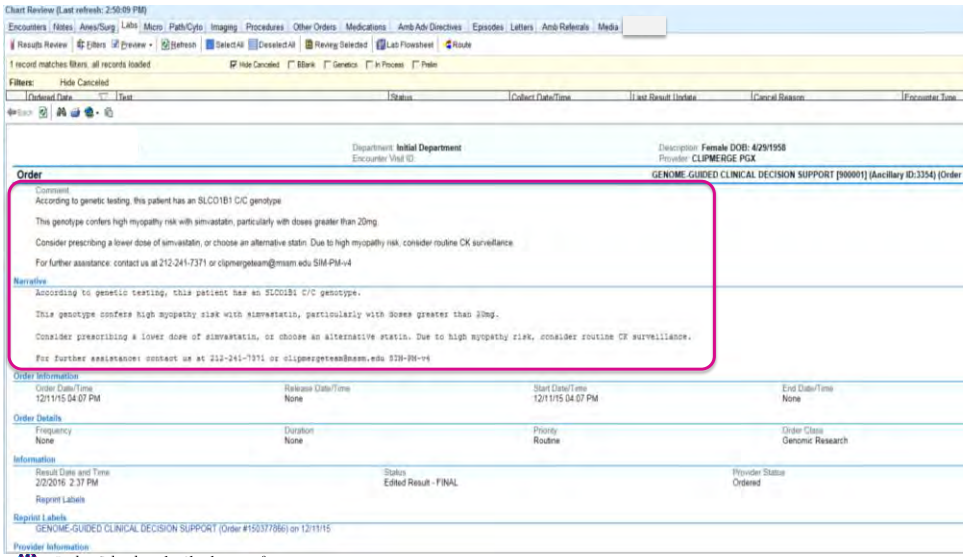


# Simvastatin Alert in EMR






# Simvastatin Alert in EMR



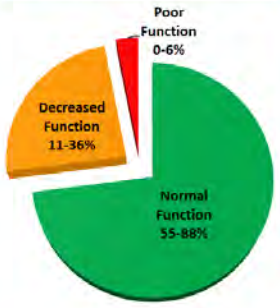
## Things To Remember:

- ⇒ *SLCO1B1* regulates the amount of simvastatin removed from the body.
- ⇒ Some *SLCO1B1* forms, caused by changes in the gene, may reduce the amount of simvastatin removed from the body leading to increased risk of drug-related muscle damage.
- ⇒ Other medications may also affect your response to simvastatin. Therefore, it is important to let your physician know all the medications that you are taking so that any potential interactions may be avoided.

## Glossary

- ⇒ **Active drug:** the form of the drug that produces the effects in the body.
- ⇒ **Enzyme:** a protein that breaks down a drug
- ⇒ **General population:** a group of people made up of different races/ethnicities
- ⇒ **Metabolism:** the breakdown of a drug
- ⇒ **Prodrug:** the inactive form of a drug which needs to be activated in the body before it can produce the desired effect

## Breakdown Of *SLCO1B1* Protein Transporter Activity In The General Population




*"One size does not fit all."*

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# Simvastatin and *SLCO1B1*

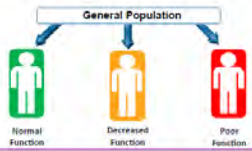
Mount Sinai

## Pharmacogenetics: *SLCO1B1*

- Pharmacogenetics is the study of how your genes affect the medications you take.
- Genes are the instruction manuals contained in each person's body.
- The instructions the body receives from the genes are what control how we look, how to grow, and how we function.
- They also contain instructions for how to make enzymes, which are proteins the body use to break down or "metabolize" what we take in, including medications.
- Changes in some genes may result in different instructions for how to make the enzymes. This could result in the body having a different form of the enzyme that may break down medications differently.
- *SLCO1B1* is a protein transporter that is responsible for clearing simvastatin from the body. Changes in the *SLCO1B1* gene lead to different forms of the *SLCO1B1* protein; which affects the way your body removed simvastatin from the body.

### Simvastatin (Zocor®)

- Simvastatin is a medication used for reducing cholesterol levels in the body.
- Its concentration in the body is regulated by *SLCO1B1* transporter protein.
- Changes in *SLCO1B1* can lead to reduced amount of simvastatin removed from the body. This can lead to increased risk of muscle damage.




### Personalized Medicine at Mount Sinai

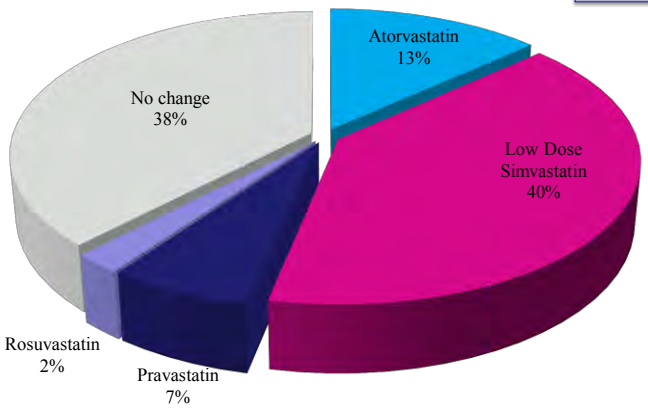
- The *SLCO1B1* genetic test provides information that helps to predict the risk of muscle damage in patients beginning simvastatin.
- In Mount Sinai's pharmacogenetics program, your genetic test results including your *SLCO1B1* results are added to the electronic medical records.
- If you have a decreased function or a poor function in *SLCO1B1*, your doctor will receive an alert when prescribing simvastatin for you.
- This alert will tell the doctor to lower the dose of simvastatin or change to another medication. **(see table below).**

**Table: *SLCO1B1* transporter protein forms and their effects on the risk of muscle damage**

| Classification | Protein Activity | Clinical Relevance |
|---|---|---|
| Normal Function | Simvastatin is removed from the body normally | Normal risk of muscle damage |
| Decreased Function | Reduced amount of simvastatin is removed from the body | Moderate risk of muscle damage |
| Poor Function | Very little amount of simvastatin is removed from the body | High risk of muscle damage |

# Therapy Changes to Simvastatin BPAs

**62.2%** Acceptance of PGx Recommendations




n = 45 BPAs

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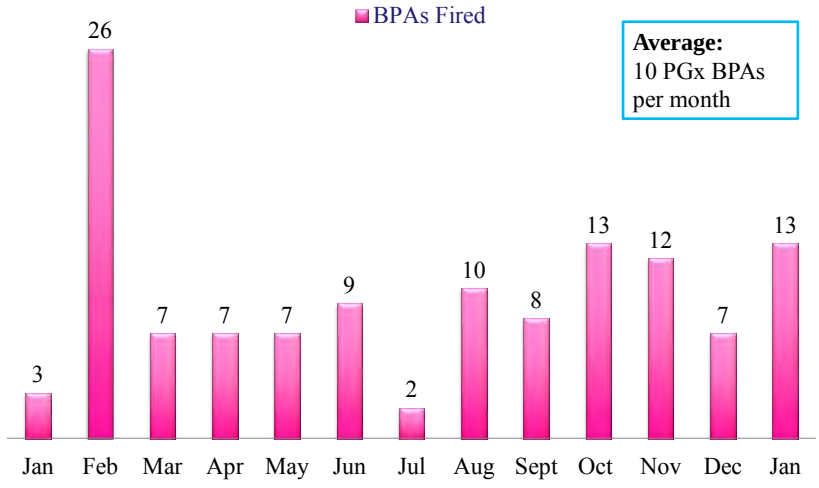
# Jan 2015 - Jan 2016

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# Accomplishments So Far…

- Creation of CLIPMERGE platform
- Established an interface with MGTL and capacity to expand NYS DOH-approved PGx genotyping panel
- Successful ROR of PGx results into Epic
- Clinical Implementation of PGx
  - Extended across Mount Sinai Hospital ambulatory clinics
  - PGx education for MDs (in-person and video)
  - Patient education brochures
- Ongoing participation in eMERGE-PGx
- Education
  - Established an elective PGx rotation



# PGx Implementation Team

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# Acknowledgements

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# QUESTIONS?

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# THANK YOU

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