U.S. Department of Veterans Affairs
Veterans Health Administration
PBM Academic Detailing Services

CLINICIAN GUIDE

Applying Pharmacogenomics (PGx) to Manage Statin-Associated Musculoskeletal Symptoms (SAMS)

PGx testing can be part of an overall strategy to find more tolerable statin options in patients experiencing SAMS

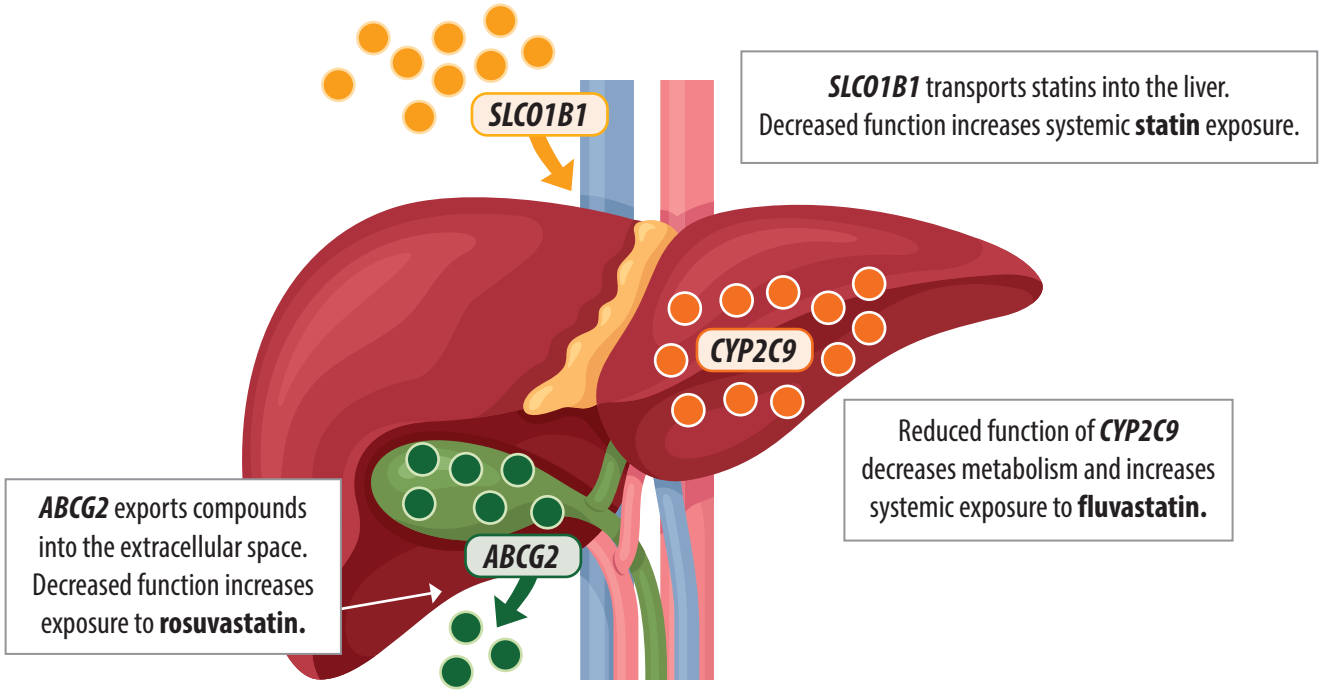
SAMS are the most common side effects cited for statin therapy discontinuation.[1] Discontinuation of statin therapy has been associated with a 36% higher rate of recurrent myocardial infarction and a 43% higher rate of coronary heart disease.[2]

Integrating PGx testing into SAMS management

PGx testing can identify if a patient has genetic variations affecting statin metabolism and may be a useful tool when selecting a statin or statin dose for rechallenge.

- Variations in the *SLCO1B1* transporter gene may further increase the plasma concentrations of all statins.[3]
- Variations in the *ABCG2* transporter gene and in *SLCO1B1* function may further increase the risk of SAMS with rosuvastatin use.[3]
- Variations in the *CYP2C9* enzyme and in *SLCO1B1* function may further increase the risk of SAMS with fluvastatin use.[3]

Figure 1. Genetic variation in transporter and enzyme function can increase the risk of SAMS

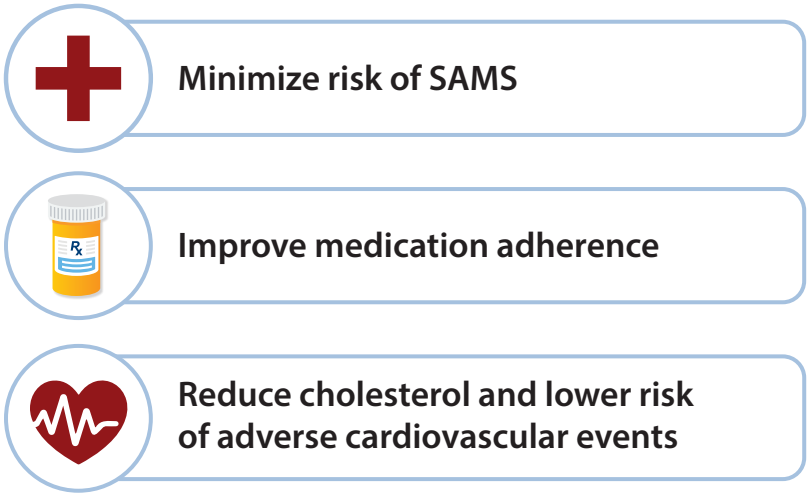


Additional factors to consider

- **There are several factors in addition to pharmacogenomics known to influence a patient's risk for developing SAMS,** e.g., high-dose statin therapy, drug interactions, etc.
- Statins are commonly prescribed in the Veteran population and incidental drug-gene interactions may be identified when ordering PGx testing for another indication. **A finding for a patient on chronic statin therapy who has not experienced SAMS may not require adjustment.** *See Table 2 for further guidance.*

See the
Academic Detailing Management of Statin Intolerance Fact Sheet
(https://tinyurl.com/9nbkxk4f) for more information on other intolerance management strategies.

Potential benefits of PGx testing for patients with a history of statin intolerance



Utilize PGx testing to identify and address a potential cause of SAMS in patients with continued need for statin therapy.

Table 1. Therapeutic consequences of variable *SLCO1B1* function and recommended adjustments for patients experiencing SAMS[3,4]

SLCO1B1 function	Therapeutic consequence	Recommendation for high-intensity statin therapy[+]	Recommendation for moderate-intensity statin therapy[+]
Increased or normal function	Typical myopathy risk/statin exposure	Prescribe desired starting dose and adjust based on disease-specific guidelines	
Decreased or possible decreased function	⬆ Plasma concentrations compared to normal function ⬆ Risk of toxicity/ SAMS compared to normal function	**Risk of SAMS** • **Lowest:** rosuvastatin 20 mg • **Moderate:** atorvastatin 40 mg rosuvastatin 40 mg • **Highest:** atorvastatin 80 mg	**Risk of SAMS** • **Lowest:** atorvastatin 10-20 mg pitavastatin 1 mg pravastatin 40 mg rosuvastatin 5-10 mg • **Moderate:** fluvastatin 80 mg pitavastatin 2 mg pravastatin 80 mg • **Highest:** lovastatin 40-80 mg pitavastatin 4 mg simvastatin 20-40 mg
Poor function	⬆⬆ Plasma concentrations compared to normal/decreased function ⬆⬆ Risk of toxicity/ SAMS compared to normal/decreased function	**Risk of SAMS** • **Lowest:** rosuvastatin 20 mg • **Highest:** atorvastatin 40-80 mg rosuvastatin 40 mg	**Risk of SAMS** • **Lowest:** atorvastatin 10-20 mg pitavastatin 1 mg pravastatin 40 mg rosuvastatin 5-10 mg • **Moderate:** fluvastatin 80 mg pravastatin 80 mg • **Highest:** lovastatin 40-80 mg pitavastatin 2-4 mg simvastatin 20-40 mg

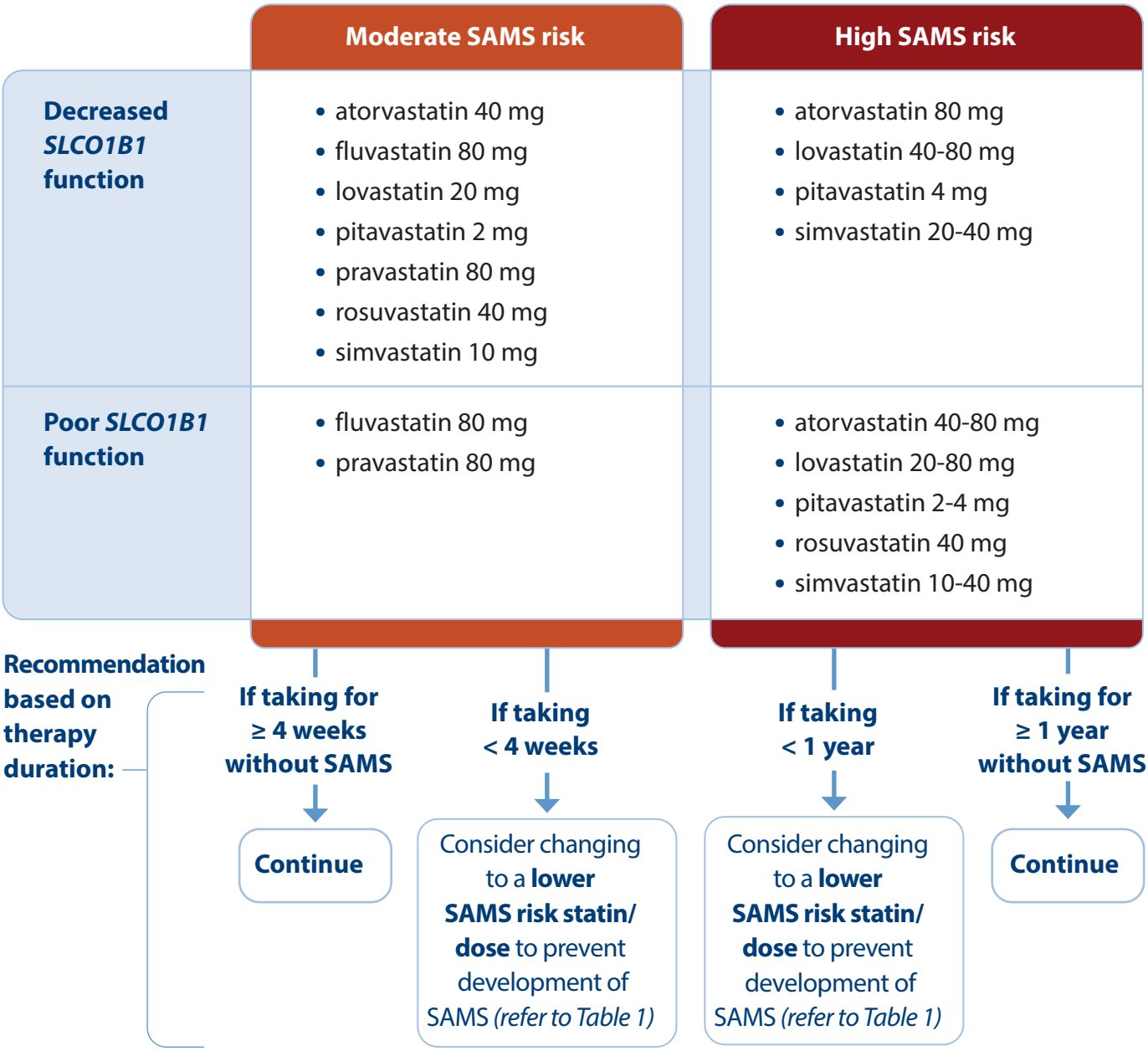
See *CPIC guidelines* (https://cpicpgx.org/guidelines/) for recommended dosing for combined *SLCO1B1* and *ABCG2* (rosuvastatin) or *SLCO1B1* and *CYP2C9* (fluvastatin) results or consult your PGx Clinical Pharmacist Practitioner.

[+]High-intensity statin therapy, as defined by the American College of Cardiology/American Heart Association, is statin therapy with a ≥ 50% LDL lowering effect. Moderate-intensity statin therapy is defined as statin therapy with a 30-49% LDL lowering effect.[4]

There has been no demonstrated increased risk of SAMS with up to 20 mg of rosuvastatin in patients with decreased or poor *SLCO1B1* function.[5]

This rosuvastatin dose is recommended for patients with an indication for moderate or high-intensity statin therapy.[4]

Table 2. Guidance for incidental findings in patients already on statin therapy without incidence of SAMS[3]



Clinical pharmacist practitioners (CPP)

PGx CPPs are Advanced Practice Providers who are highly trained members of the healthcare team with additional education or experience in pharmacogenomics.

Consult services are available in the electronic medical record orders package for providers to request CPP assistance. CPPs can evaluate statin pharmacotherapy based on the PGx test results, make adjustments if needed, and contact patients for follow-up education.

REFERENCES: 1. Cohen JD, et al. Understanding Statin Use in America and Gaps in Patient Education (USAGE): an internet-based survey of 10,138 current and former statin users. *J Clin Lipidol.* 2012;6(3):208-215. **2.** Serban M-C, et al. Statin Intolerance and Risk of Coronary Heart Events and All-Cause Mortality Following Myocardial Infarction. *J Am Coll Cardiol.* 2017;69(11):1386-1395. **3.** Cooper-DeHoff RM, et al. The Clinical Pharmacogenetics Implementation Consortium Guideline for SLCO1B1, ABCG2, and CYP2C9 genotypes and Statin-Associated Musculoskeletal Symptoms. *Clin Pharmacol Ther.* 2022;111(5):1007-1021. **4.** Grundy SM, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2019;73(24):3168-3209. **5.** Danik JS, et al. Lack of association between SLCO1B1 polymorphisms and clinical myalgia following rosuvastatin therapy. *Am Heart J.* 2013;165(6):1008-1014.