PCSK9 Inhibitors for Treatment of High Cholesterol

Action Guide and Resource Compendium

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About this Guide & Table of Contents

This Action Guide and Resource Compendium provides a list of recommendations and resources to support clinicians, provider organizations, and policymakers in implementing use of PCSK9 inhibitors. It is intended to serve as a companion document to policy recommendations presented in the ICER report, *PCSK9 Inhibitors for Treatment of High Cholesterol*. The full report and additional materials are available on the CEPAC website.

How to use this Action Guide: Each section contains one or more key recommendations from the report, accompanied by resources to provide further background and implementation support to help stakeholders translate and apply the guidance to practice and policy.

A more detailed explanation of the recommendations contained within this guide is presented in section 7 of the ICER report.

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Clinical Effectiveness

In July and August of 2015, the FDA approved two new agents for treatment of high cholesterol: PCSK9 inhibitors **alirocumab** (Praluent®, Regeneron/Sanofi) and **evolocumab** (Repatha™, Amgen).

Effect: While early evidence suggests that PCSK9 inhibitors are effective in lowering LDL-C, there is still limited research available on their long-term outcomes. Long-term studies will assess the drugs' effects on cardiovascular event outcomes. As a result, their long-term benefits, as well as information about adverse events associated with the drugs, are still unclear.

ICER considers the evidence surrounding PCSK9 inhibitors to be "promising but inconclusive."

Image Sources:
http://www.bizjournals.com/losangeles/news/2015/08/28/amgen-wins-fda-approval-for-cholesterol-drug.html#i1
http://www.theindependentbd.com/printversion/details/10042

Value and Value-Based Price Benchmarks

Costs: PCSK9 inhibitors carry high price tags. Praluent has a wholesale acquisition cost of $14,600, while Repatha is priced at $14,100. For the purposes of ICER's review, these costs were averaged for a WAC of $14,350.

Potential Budget Impact: In addition to their high cost, PCSK9 inhibitors have a potentially large eligible patient population.

The table at right provides **value-based price benchmarks.** The value based price benchmark considers the price at which the drug would meet commonly accepted cost-effectiveness thresholds, as well as an analysis of the potential short-term budget impact. The value-based price benchmark represents the price needed to remain within accepted thresholds. Any price beyond the benchmark will likely create a need for extra mechanisms to manage affordability. Details of the assumptions and calculations that go into our value-based price benchmarks are available on ICER's website.

For PCSK9 inhibitors, the value-based price benchmark represents a reduction of 85% from the average wholesale acquisition price of the two agents.

PCSK9 Value Based Price Benchmarks				
Population	Care Value Price: $100K/QALY	Care Value Price: $150K/QALY	Max Price at Potential Budget Impact Threshold	Draft Value-Based Price Benchmark
TOTAL (n=2,636,179)	***$5,404***	***$7,735***	***$2,177***	***$2,177***

Recommendation: Use prior authorization criteria to limit use to populations with highest unmet need

Recommendation: Payers should use prior authorization to enhance health system value by limiting treatment to patients for whom extended trials of high-dose statins combined with ezetimibe have been unsuccessful.

The coverage policy at right provides sample language for prior authorization criteria.

Prior Authorization Policy Example: Anthem's Policy for Coverage of Alirocumab	
1.	Patient must have HoFH, HeFH, or ASCVD
2.	Patient must be on a high intensity statin (atorvastatin 40mg or rosuvastatin 20mg), or on a maximally tolerated statin dose This requirement is waived in cases of contraindication or statin intolerance. For more information on criteria for statin intolerance, see page 8 of this guide.
3.	Patient must be taking ezetimibe, in addition to maximally tolerated statin dose.
4.	Despite treatments for at least 90 days with optimal compliance, patient's LDL-C level must continue to fall above target. Target is defined as less than a 50% reduction in LDL-C levels. For patients with no baseline LDL-C measurement, target is defined as <70mg/dL for patients with CVD, or <100mg/dL for patients with no history of CVD.
View Anthem's full coverage policy here.	

Prior Authorization Consideration: Relax criteria for patients with FH

When developing prior authorization policies, special considerations may be needed for individuals with familial hypercholesterolemia.

Individuals with FH whose cholesterol levels are not at goal may be at higher risk than other populations due to their long-term exposure to high cholesterol since early on in life. Some patients with FH must endure intensive and expensive treatment to manage their LDL-C. PCSK9 inhibitors offer a new treatment option for individuals with FH for whom there is currently a critically unmet need.

The resources at right provide more information about FH.

About FH	
What You Need to Know: Familial Hypercholesterolemia	Patient information about FH from the National Lipid Association Foundation.
FH Patient Tear Sheet	Provide your patients with a completed copy of this information sheet so that they can join the FH registry.
FH Registry	Encourage patients with FH to join the FH registry.
Diagnosis and Management of FH	Information about managing FH to share with patients.

Prior Authorization Consideration: Optimize statin therapy and adherence

When identifying appropriate treatment for management of LDL-C, it is important to ensure that statin therapy is optimized before exploring alternative therapies. Adherence is an essential component of ensuring optimization. The resources below provide strategies to improve patient adherence.

Tools to improve patient adherence:	
Clinician's Toolkit: A Guide to Medication and Lifestyle Adherence	Toolkit for clinicians to identify issues and improve adherence.
Noncompliance With Lipid-Lowering Therapy: How to Improve Compliance	Medscape article on compliance strategies (log-in required).
Medication Adherence - Improving Health Outcomes	A resource from the American College of Preventive Medicine.
National Lipid Association Educational vClinic	A series of videos intended to support strategies to improve patient adherence to lipid lowering therapies, including the diagnosis and treatment of statin intolerant patients, and to overcome barriers to due statin intolerance, perceived risk for side effects, and/or treating existing side effects.

Statin Specific Adherence Measures

A number of methods for measuring adherence have been cited in peer-reviewed literature. These were not assessed in ICER's report but may be useful to clinicians.

Some methods for measuring statin adherence may include:

- Observing treatment
- Measuring the concentration of the drug in blood or urine.
- Questionnaires
- Pill counts
- Prescription refill rates
- Measurement of physiological markers (e.g. LDL-C levels)
- Encouraging use of a medication diary
- Electronic medication monitoring

Recommendation: Re-try previously intolerant patients on statins when appropriate

Recommendation:
Prior authorization criteria may need to require most patients who believe they are statin intolerant to be re-tried on statins.

The resources at right provide further information about statin intolerance. The following page contains additional tools and resources for identifying and managing intolerance.

Definitions of Statin Intolerance	
National Lipid Association Statin Intolerance Panel	1. Patient has been unable to tolerate at least 2 statins, with one of them at the lowest possible dose 2. Dose reduction, as opposed to discontinuance of therapy, has been tried for resolution of symptoms and biomarker abnormalities. 3. Symptoms and biomarker changes are reversed when statin use is stopped. They are reproduced when statins are re-started. 4. Symptoms or biomarker abnormalities are not attributable to established predispositions or conditions recognized to increase the risk of statin intolerance
International Lipid Expert Panel	The inability to tolerate at least 1 statin at any dose or an increase in dose above pre-determined weekly maximum doses because of intolerable myalgia (muscle pain, soreness, weakness, or cramps) or myopathy (myalgia plus elevated creatine kinase [CK]) and having symptom improvement or resolution with statin discontinuation.

When is a statin re-challenge clinically appropriate?
According to the NLA Panel, statin re-challenge may be appropriate for individuals who:
• Are symptomatic
• Have creatine kinase less than four times the upper limit of normal per laboratory reference range
• Have AST/ALT less than three times the upper limit of normal per laboratory reference range

Statin Intolerance: Attempt to manage symptoms before diagnosing intolerance

Additional information about statin intolerance, as well as tools for assessment, are available at right.

Information on statin intolerance:	
American College of Cardiology's Statin Intolerance Tool	An algorithm for assessing and identifying statin intolerance.
Cleveland Clinic Patient Education Videos	Videos on a variety of topics related to cardiovascular health. Scroll to “Medications” tab for videos on statins and statin intolerance.
Statin Intolerance Information from Rx Files	Guidelines for assessing statin intolerance and adjusting medication to manage intolerance.
Cleveland Clinic: Statin Medications & Heart Disease	Cleveland Clinic information on statins and statin intolerance.
Treatment strategies in patients with statin intolerance: the Cleveland Clinic experience	A peer-reviewed article from the Cleveland Clinic addressing treatment strategies for patients with statin intolerance.
NLA Lipid*Spin:* Statin Intolerance	A publication by the National Lipid Association with a focus on statin intolerance, including tools and strategies for managing symptoms of intolerance.

Recommendation: Adopt LDL-C targets in clinical guidelines

Recommendation: Professional societies should take prompt action to update clinical guidance, including a likely need to return to treatment goals based on target LDL-C levels.

An updated guideline that stratifies patients by their cardiovascular risk, includes treatment goals based on target LDL-C levels, and titrates medication use to reach a specified target would provide clinicians with a basis for discussion when examining treatment options with patients.

The resources at right support the use of LDL-C goals in managing high cholesterol.

Guideline Resources	
New Therapies in the Treatment of High Cholesterol: An Argument to Return to Goal-Based Lipid Guidelines	A *JAMA* article reviewing the need to return to goal-based treatment of high cholesterol.
National Cholesterol Education Program: ATP III Guidelines At a Glance	An at-a-glance summary of ATP III guidelines. LDL-C goals and treatment strategies are stratified by level of risk.

Example: American Association of Clinical Endocrinologists Guideline

Risk Category	Characteristics	LDL-C Goal
Very High	CVD or diabetes, in addition to one or more other risk factors	<70mg/dL
High	At least 2 risk factors and 10-year risk over 20%, or CHD risk equivalents (e.g. diabetes with no other risk factors)	<100mg/dL
Moderately High	At least 2 risk factors and 10-year risk between 10% and 20%	<130mg/dL
Moderate	At least 2 risk factors and 10-year risk below 10%	<130mg/dL
Low	One or no risk factors	<160mg/dL

Recommendation: Restrict prescribing capabilities to specialists

Recommendation: Management of patients with possible statin intolerance and other complexities of decision-making regarding PCSK9 inhibitors suggest that it is reasonable to restrict prescribing of PCSK9 inhibitors to specialists in lipid management.

The coverage policies listed at right provide and example of a regional and a national private payer limiting prescribing to specialist providers.

Examples of Health Plans Currently Requiring Specialist Prescriptions:	
Blue Cross Blue Shield of Vermont	Initial prescription must come from a cardiologist. Prescriptions may be renewed by another physician if in consultation with a cardiologist.
United Healthcare	The drugs must be prescribed by a cardiologist, endocrinologist, or lipid specialist.

Recommendation: Align benefits of drug with affordability

Recommendation: If the pricing for PCSK9 inhibitors were to fall 50%-85% to a level that aligns with the benefit to patients and with a reasonable short term affordability, payers would likely consider lifting many elements of proposed prior authorization requirements.

Information on value-based pharmaceutical pricing	
Performance-Based Risk-Sharing Arrangements—Good Practices for Design, Implementation, and Evaluation	Report of the ISPOR Good Practices for Performance-Based Risk-Sharing Arrangements Task Force.
Private Sector Risk-Sharing Agreements in the United States: Trends, Barriers, and Prospects	A report from AJMC on risk-sharing agreements.
Value-based pricing for pharmaceuticals: Implications of the shift from volume to value	A report from Deloitte on value-based pricing.

Existing Value Based Payment Design	
Harvard Pilgrim Pay for Performance Agreement with Amgen	Harvard Pilgrim Health Care negotiated a discounted payment rate as well as the first pay-for-performance contract for Amgen's PCSK9 inhibitor Repatha. The drug will be included on HPHC's formulary at a reduced price. In addition, Amgen will provide additional rebates if the drug doesn't reduce cholesterol to specified target levels for eligible patients. Amgen may also pay out rebates if more patients covered by HPHC's plans end up taking the drug than was initially projected. The exact terms of the agreement including the level of discount and rebate amounts are not publicly available at this time.
For more information on the agreement: • Harvard Pilgrim strikes 'pay-for-performance' deal for cholesterol drug, Boston Globe • Harvard Pilgrim cements risk-based contract for pricey cholesterol drug Repatha, Modern Healthcare	

Future Research Needs

Recommendation: Future research needs will be strongly influenced by the results of current clinical outcomes studies, but additional research in adherence and long-term safety will be important to guide practice and policy in the future.

Research Areas
• Results from long-term outcomes trials are expected in 2017. These trials will provide greater clarity on the long-term clinical benefit and adverse event rates associated with PCSK9 inhibitors.
• There may also be a need to examine real world data related to difference in treatment adherence between PCSK9 inhibitors and statins.
• There may be opportunity to develop tools to help physicians educate patients about statin intolerance.