USC School of Pharmacy
USC Schaeffer
Leonard D. Schaeffer Center for Health Policy & Economics

FH FOUNDATION
Raising Awareness. Saving Lives.

Cost-effectiveness of Screening and Management Strategies for Familial Hypercholesterolemia in the United States: an Update

Zawadzki NK[1], Hay JW[1], Ahmed CD[2], Myers KD[2], Gidding SS[2]

[1]Department of Pharmaceutical and Health Economics, School of Pharmacy, University of Southern California (USC), Los Angeles, CA, USA, [2]The FH Foundation, Pasadena, CA, USA

OBJECTIVES

- Is genetic cascade screening for heterozygous FH cost-effective in the US compared with routine lipid cascade screening?
- Is the addition of PCSK9i in combination with statin therapy for high cholesterol cost-effective in the US heterozygous FH population?

This study aimed to provide an update of a previous model estimating the cost-effectiveness of genetic screening and lipid-based screening with intensive therapy (statin + PCSK9i therapy) compared to lipid-based screening (statin therapy alone) in the US.

METHODS

This analysis is based on a previous model,[7] adjusted for changes in the treatment cost and effect of statin + PCSK9i therapy and the cost of genetic screening.

Perspective: US societal

Transition Probabilities (Table 1)

- Statin and PCSK9i efficacy parameters[10-14] and the proportion diagnosed based on the decision tree were used to adjust cholesterol levels from baseline and calculate risk of major events and death.
- Adjusted cholesterol levels and Framingham Heart Study[15-16] risk equations were used to generate the 10-year probability of CVD and the 10-year probability of CVD-related death by male age groups, in 10- year intervals, converted into 1-year health state transition probabilities using the DEALE method.
- Transition probabilities for death after a CVD event were estimated by multiplying probability of CVD-related death with the hazard ratio of death after an event, assumed to be 5.00 based on US studies that provide long-term survival prognosis 5 to 10 years after AMI or stroke in the Framingham Heart Study population.[15-16]

Table 1. Transition Probability Adjustment Base Case Parameters

Parameter	Effect, Point Estimate (Range)
Hazard ratio of death after AMI [15-16]	5.0
Odds ratio of adherence [17]	1.38
Effect of Statin Therapy [10-11]	
Decrease in LDL-C [a]	38.0% (35.7–40.3)
Increase in HDL-C [b]	5.50% (2.75–8.25)
Additional Effect of PCSK9i [21]	
Decrease in LDL-C [a]	55.0% (60.2–51.3)
Increase in HDL-C [b]	9.0% (7.5–11.4)
Baseline Adherence to Statin Therapy [13-14]	
Percent adherent 1-9 years of therapy	56.0% (12.0–94.0)
Percent adherent 10+ years of therapy	42.0% (0–90.0)

a Low-density lipoprotein cholesterol
b High-density lipoprotein cholesterol

Selected Input Costs (Table 2): Costs were evaluated and reported from a US societal perspective and adjusted to 2013 US dollars using the CPI for Medical Care, when needed.

Table 2. Select Input Costs

SCREENING COSTS	
Gene sequence of index case [9]	$250
DNA mutation test for FH [9]	$250
Direct LDL-C test [18]	$17
TREATMENT AND ADHERENCE COSTS [19-21]	
Annual statin therapy	$42
Annual statin adverse events	$186
Annual PCSK-9 therapy [22]	$1,500
CVD AND STROKE COSTS [23-24]	
1st year cost of AMI[a]	$23,123
Annual cost of AMI (ongoing)	$3,703
1st year cost of angina	$8,139
Annual cost of angina (ongoing)	$3,536
1st year cost of stroke	$16,044
Annual cost of stroke (ongoing)	$2,392

a Acute myocardial infarction

Input Health-State Utilities (Table 3): Utilities for each state in the Markov model were estimated from studies using a US societal perspective, with reference to perfect health utility of 1 and death state utility of 0.

Table 3. Input Health-State Utilities

Asymptomatic CVD[a] [25]	0.996
CVD Event/Stroke [26]	0.704
Death	0

a Cardiovascular disease

CONTACT

Email: zawadzki@usc.edu
Phone: (650) 319-5898

BACKGROUND

- Heterozygous familial hypercholesterolemia (FH) is a **genetic disorder** that affects approximately **1 in 250** individuals in Western populations (Figure 1).[1]
- In individuals with FH, **mutations in the genes** responsible for plasma low-density lipoprotein cholesterol (LDL-C) clearance cause **abnormal accumulation of cholesterol in the blood** and **premature cardiovascular disease (CVD)**.[1-3]
- Treatments have been shown to be highly effective, but **fewer than 20% of US FH cases are diagnosed and fewer than 50% of US adults receive treatment** for high cholesterol.[1]
- **Under-diagnosis is the largest barrier to FH care** as clinical manifestation is most often characterized by initial acute myocardial infarction (AMI) or stroke (Figure 2, Figure 4).[1]
- Options for diagnosis are (1) **clinical criteria**, based on a combination of high cholesterol, presence of tendon xanthomata in the patient or first-degree relative, and a family history of premature CHD or high cholesterol; or (2) **genetic screening** through a DNA test to identify the causative mutation.[1]
- An index diagnosis of FH followed by **family (cascade) screening** of relatives is considered the most efficient method of identifying additional cases given the autosomal-dominant inheritance of FH.[1]
- Many European countries have established guidelines for cascade screening that often involve genetic testing, but **no formal guidelines exist in the US**.[3-7]
- Previous studies found that genetic screening for FH with subsequent statin therapy is not cost-effective in the US.[3]
- In 2015, **proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i)** were newly approved in the US for treatment in FH individuals,[8] and since 2015, the cost of genetic testing has **decreased by more than 10-fold**.[9]

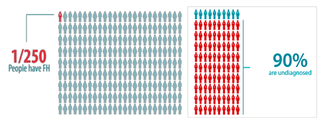


Figure 1: Estimated Prevalence Rate and Undiagnosed Rate for FH

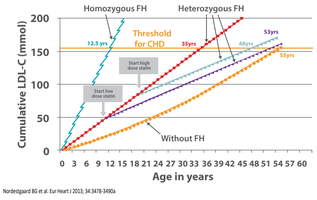


Figure 2: LDL-C Levels by Age for FH and Non-FH Individuals

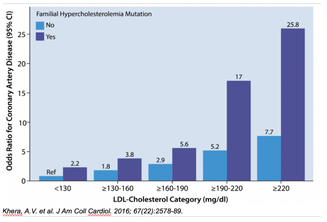


Figure 3: Impact of FH Mutation Status on CHD According to LDL-C Level

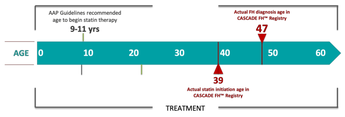


Figure 4: CASCADE FH™ Registry Data Shows Gap in Diagnosis & Treatment from Guidelines

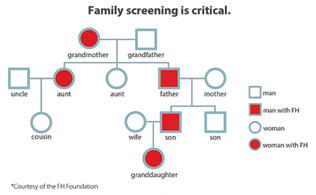


Figure 5: Diagram of FH Inheritance

MODELS

[a] Quality adjusted life-years
[b] Incremental cost-effectiveness ratio

Initial cohort: 1000 Caucasian male adults with a family history of FH and high-risk serum cholesterol levels.

A **decision tree** was used to estimate disease detection with the three screening strategies (Figure 6).

A **Markov model** was used to model disease progression until death, quality-adjusted life years (QALYs) and costs from a US societal perspective (Figure 7).

Table 4. Base Case Patient Cohort* (n = 1000)

Median Age	43.1
HDL cholesterol[a]	46 mg/dL
LDL cholesterol[b]	224 mg/dL

* Adapted from the study population for the UK's Simon Broome Register of Familial Hyperlipidaemia
a High-density lipoprotein
b Low-density lipoprotein

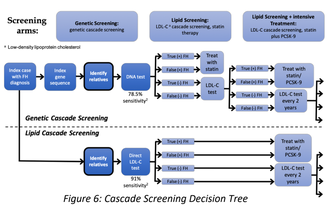


Figure 6: Cascade Screening Decision Tree

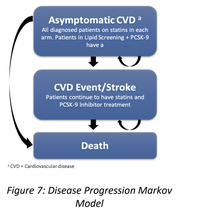


Figure 7: Disease Progression Markov Model

RESULTS

- **Genetic screening with statin therapy is cost-effective** at a US willingness-to-pay threshold of $150,000 per QALY (Table 5).
- Although lipid screening with subsequent statin + PCSK9i therapy incurs more lifetime costs than lipid screening with statin therapy alone or genetic screening with statin therapy in FH, it **provides the most incremental benefits** within the willingness-to-pay threshold (Figure 8).

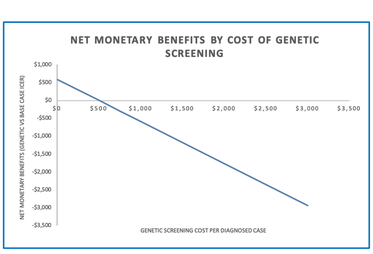


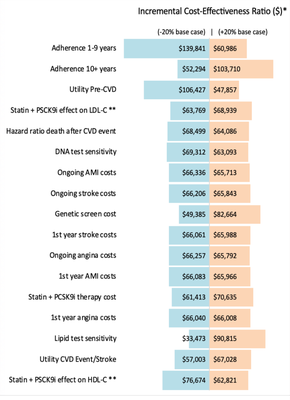
Figure 8: Net Monetary Benefits of Genetic Screening

Table 5. Markov Model Results

	Total Costs	Total QALYs	Incremental Cost	Incremental QALYs	ICER ($/QALY)
Lipid screening & statin therapy (reference)	$14,750	18.903	--	--	--
Genetic screening & statin + PCSK9i therapy versus reference	$14,984	18.907	$234	0.004	$66,024
Lipid screening & statin + PCSK9i therapy versus genetic screening	$25,700	19.658	$10,717	0.751	$14,268

RESULTS (continued)

- **ICER results were robust in one-way sensitivity analysis**
- Results were most sensitive to **adherence parameters, utility pre-CVD**, and **statin + PCSK9i effect on LDL-C.**



*Base case ICER for genetic screening & statin + PCSK9i therapy versus lipid screening & statin therapy = $66,024; upper bound = +20% base case; lower bound = -20% base case.
** Statin + PCSK9i effect parameters varied by -7.5% and +7.5% base case.
Note: is not clear that lowering LDL-C more than 93% (base case) improves CVD risk. [27]
a Cardiovascular disease
b High-density lipoprotein cholesterol
c Low-density lipoprotein cholesterol

Figure 9: One-way Sensitivity Analysis Results

LIMITATIONS

- This study is limited mainly by the lack of data available on diagnosis and treatment of the US FH patient population.
- The limited risks available in published literature at the time of this study allowed only for a greatly simplified Markov model of CVD progression, which does not include separate states for secondary events and treatment.
- Additionally, this study examines disease progression in a male population only, and may not be directly generalizable to the entire FH population in the US.
- Further, there exist substantial gaps in knowledge regarding genetic screening and disease management for FH patients in the US. As a result, European data was used to inform the genetic cascade screening program modeled in this study.

CONCLUSIONS

- Because of falling screening costs, **genetic cascade screening for FH is now generally cost-effective in the US**.
- Aggressive LDL lowering with **statin + PCSK9i therapy is a cost-effective way to improve health outcomes** for FH patients.
- However, much additional information is needed in order to suggest further policy implications, including
  - More thorough FH registries in the US.
  - Large sample genetic testing for FH in the US.
  - Long term, randomized studies of adherence and outcomes.
- Because FH patients face a lifetime of elevated LDL-C levels, efforts and resources can be directed towards increased screening and improved, sustained adherence to statin, PCSK9i and other lipid-lowering treatments to help improve health outcomes for these individuals.

REFERENCES

DISCLOSURES

Authors have no conflicts to disclose.