MyCardioAdvocate™

Familial Hypercholesterolemia (FH)

When inherited cholesterol goes undiagnosed for generations

Updated March 2026 — Reflects the 2026 ACC/AHA/NLA Dyslipidemia Guidelines

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Why This Matters

Familial Hypercholesterolemia (FH) is a genetic condition that causes extremely elevated cholesterol from birth. If you inherit even one mutated gene for LDL receptor defects, cholesterol metabolism goes awry — your LDL-C stays high no matter what you eat or how much you exercise. Without treatment, men with FH have a **50% risk of heart attack by age 50**; women face similar risk by age 60.

FH affects approximately **1 in 250 to 500 people** — making it one of the most common genetic disorders. Yet **over 90% of people with FH are undiagnosed**. They're dismissed as having "high cholesterol" without realizing it's genetic, heritable, and requires aggressive treatment. Generations of families unknowingly carry this risk.

The 2026 guidelines mark a watershed moment: genetic testing for FH is now **Class I (B-NR)** — the strongest recommendation — for anyone with possible, probable, or definite FH. This is a sea change from previous guidelines that treated FH primarily as a clinical diagnosis.

Why FH Flies Under the Radar

FH is a genetic diagnosis that masquerades as "bad lifestyle" and "high cholesterol." This misidentification costs lives:

- **Affects 1 in 250–500 people, yet >90% are undiagnosed** — Most people with FH have never heard the term. They think their high cholesterol is their fault (diet, exercise, weight) rather than recognizing it's genetic and requires genetic treatment.
- **Often dismissed as "just high cholesterol"** — A patient presents with LDL-C of 200 mg/dL and is told to "cut fat and exercise." No one asks: are your parents hypertensive? Did a relative have a heart attack before age 60? Is there a family pattern? These questions reveal FH.
- **LDL-C >190 in a young person should trigger FH evaluation** — But it often doesn't. Statins are started, but if the family history isn't explored, FH goes unrecognized. This delays more aggressive therapy.
- **Standard risk calculators are HARMFUL for FH patients** — This is critical. The 2026 guidelines assign a **Class III: Harm (COR 3)** rating to using PCE or PREVENT in FH patients. Why? Because a 35-year-old with FH may score as "low 10-year risk" on a standard calculator — leading a well-intentioned doctor to withhold statins. This is dangerous.
- **Physical findings often missed** — Tendon xanthomas (fatty lumps on the Achilles tendon or extensor tendons of the hand) are pathognomonic for FH but are rarely examined for. Corneal arcus (a white ring around the cornea) is also specific. Most doctors don't look.
- **Children are often not treated early** — FH runs in families, yet cascade screening of siblings and children is inconsistently done. Children with FH who are identified early can benefit from decades of preventive therapy before adulthood — but if they go undiagnosed until age 40, damage is done.
- **Heterozygous vs. Homozygous confusion** — Even among clinicians, there's confusion between heterozygous FH (1 mutated gene; 1 in 250–500) and homozygous FH (2 mutated genes; 1 in 160,000–1 million). Homozygous FH is far more severe and visible in childhood.

What Changed in 2026

> **Genetic Testing for FH: Class I (B-NR)**
> The 2026 guidelines mandate genetic testing for all patients with suspected FH — whether clinical criteria are met or not. This is a major shift toward precision diagnosis.

Clinical Diagnosis Criteria (FH Score)

While genetic testing is now the gold standard, clinical criteria still guide who should be tested:

- **Definite FH (LDL-C ≥190 mg/dL OR ≥100 nmol/L):** Obtain genetic testing immediately
- **Probable FH (LDL-C 155–189 mg/dL):** With family history of early MI or ASCVD, obtain genetic testing
- **Possible FH (LDL-C 130–154 mg/dL):** With significant family history, consider genetic testing

FH-Specific Risk Scores

Standard calculators don't work for FH. Instead, use FH-specific scores:

- **Montreal-FH-SCORE:** Estimates 10-year cardiovascular risk in genetically confirmed FH patients. More accurate than PREVENT or PCE in this population.
- **FH-Risk Score:** Incorporates lipid levels, age, and genetic mutation type to stratify risk among FH patients.

Tiered Treatment Targets (LDL-C)

FH treatment is aggressive and tiered based on whether ASCVD is present:

- **Without ASCVD:** LDL-C goal <100 mg/dL (start statins around age 20; younger if family hx of early MI)
- **With risk factors (hypertension, smoking, diabetes, family hx):** LDL-C goal <70 mg/dL
- **With established ASCVD:** LDL-C goal <55 mg/dL; ApoB <55 mg/dL

Medications in FH Algorithm (2026)

- **Step 1:** High-intensity statin (atorvastatin 40-80 mg or rosuvastatin 20-40 mg)
- **Step 2 (if LDL-C not at goal):** Add ezetimibe 10 mg daily
- **Step 3 (if still not at goal):** Add PCSK9 inhibitor (evolocumab, alirocumab, inclisiran) — Class I
- **Step 4 (homozygous or very severe):** Evinacumab (APOB inhibitor) for homozygous FH or PCSK9-refractory patients
- **Inclisiran (newer):** An siRNA targeting PCSK9; administered subcutaneously every 6 months — offers convenience

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MyCardioAdvocate™ Checklist

Use these questions to diagnose FH yourself and guide the conversation with your physician.

1. Could I Have FH? Clinical Criteria

Start with clinical clues.

- ■ *Is my LDL-C ≥190 mg/dL (or ≥100 nmol/L) without familial cholesterol patterns?*
- ■ *Do I have LDL-C 155–189 mg/dL with a family history of early MI or stroke?*
- ■ *Does my family have a pattern of "high cholesterol" or heart disease before age 55 (men) or 65 (women)?*
- ■ *Do I have tendon xanthomas (bumpy deposits on the Achilles tendon or back of hands)?*
- ■ *Do I have corneal arcus (white ring around the edge of the cornea)?*
- ■ **If you answer YES to any of these, discuss FH evaluation with your doctor.**

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2. Genetic Testing

The 2026 guideline is clear: genetic testing is Class I for suspected FH.

- ■ *Has genetic testing for LDLR, APOB, or PCSK9 mutations been done?*
- ■ *If positive, do I have heterozygous FH (1 mutation) or homozygous FH (2 mutations)?*
- ■ *Are there online resources (FH Foundation, GeneFH, etc.) that explain my specific mutation?*

Heterozygous FH: 1 mutated gene; ~1 in 250–500 people. Risk of early MI if untreated.
Homozygous FH: 2 mutated genes; 1 in 160,000–1 million. Very severe; often diagnosed in childhood; MI risk in teens/20s without treatment.

- ■ **Genetic testing is NOT expensive (often covered by insurance) and is essential for diagnosis confirmation and family screening.**

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3. What Are My Treatment Targets?

FH treatment is NOT the same as treating sporadic high cholesterol.

- ■ *What is my LDL-C goal? Is it <100 (no ASCVD), <70 (risk factors), or <55 (with ASCVD)?*
- ■ *Am I on a high-intensity statin? What dose?*
- ■ *If not at goal, am I on ezetimibe?*
- ■ *If still not at goal, am I on a PCSK9 inhibitor or inclisiran?*

Target thresholds (2026):
No ASCVD: LDL-C <100 mg/dL
Risk factors present: LDL-C <70 mg/dL
Established ASCVD: LDL-C <55 mg/dL (and ApoB <55 mg/dL if possible)

> **Pro Tip:** If your doctor says "your cholesterol is controlled" at an LDL-C of 120 mg/dL and you have FH, that's not good enough. FH requires aggressive treatment. Don't settle for "normal" targets. Demand achievement of FH-specific goals.

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4. Cascade Screening for Family Members

FH runs in families. Half of your siblings and children likely carry the mutation.

- ■ *Have my children been screened? If older than 20, they should be on treatment if FH-positive.*
- ■ *Have my siblings been tested for FH?*
- ■ *Have my parents been formally diagnosed with FH, or is it just "high cholesterol"?*
- ■ *Are extended family members (cousins, uncles, aunts) aware of their cardiovascular risk?*

- ■ **Cascade screening can identify at-risk relatives before they have heart attacks. This is one of the highest-impact interventions in cardiovascular medicine.**

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5. Is Treatment Adequate and Adhered To?

Having the diagnosis means nothing without therapy compliance.

- ■ *Am I on a statin every day?*
- ■ *If prescribed additional medications (ezetimibe, PCSK9i), am I taking them consistently?*
- ■ *Has my doctor discussed the importance of lifelong treatment, even if I feel well?*
- ■ *Do I understand that stopping treatment allows cholesterol to climb back, increasing MI risk?*

- ■ **FH treatment is lifelong. Missing doses or stopping therapy undermines decades of prevention. Adherence literally saves lives.**

CPR Opportunities — Shared Decision-Making

While FH diagnosis is straightforward, certain decisions require nuanced discussion with your physician.

Genetic Testing: Diagnostic Gold Standard or Unnecessary?

The 2026 guideline strongly recommends genetic testing for all suspected FH. But some patients and doctors ask: if clinical criteria are met (LDL-C ≥190), does genetic testing change management?

- **Arguments for genetic testing:** Confirms diagnosis definitively, allows cascade screening of relatives, identifies specific mutation (informs prognosis), enables family discussions, documents heritable disease
- **Potential concerns:** Genetic testing is rarely denied insurance coverage, but psychological burden of "being labeled genetically diseased" exists for some patients

> **Applying CPR:**
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> **Calculate** — Clinical criteria alone are sufficient for diagnosis; genetic testing refines it
> **Personalize** — Consider your family structure: do you want to know your mutation to inform cascade screening?
> **Reclassify** — Genetic confirmation may allow use of FH-specific risk scores instead of standard calculators
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> *The 2026 guideline recommends genetic testing. It's accurate, affordable, and recommended Class I (B-NR).*

How Aggressive to Treat Young Adults with FH (Before Age 40)?

A 25-year-old with newly diagnosed FH and LDL-C of 210 mg/dL has high risk of MI by age 45–50 without treatment. But should treatment be "moderate" (statin alone, targeting LDL-C <100) or "aggressive" (statin + ezetimibe + PCSK9i targeting <70 or <55)?

- **Data supporting aggressive early treatment:** Every decade of exposure to elevated LDL-C increases atherosclerotic burden. Early aggressive therapy reduces lifetime MI risk by ~30–40% compared to standard therapy.
- **Shared decision-making factors:** Presence of other risk factors (smoking, hypertension, family hx of very early MI), patient motivation for treatment compliance, cost/insurance barriers, side effects

> **Applying CPR:**
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> **Calculate** — Estimate 30-year and lifetime risk using FH-specific scores (Montreal-FH-SCORE)
> **Personalize** — Does your family have a history of MI before age 45? This favors aggressive early therapy.
> **Reclassify** — Consider CAC scoring in young FH patients; if calcium is present, aggressive therapy is justified
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> *The general approach: in young FH patients, early aggressive therapy prevents decades of disease. Discuss with your doctor whether your risk profile warrants monotherapy (statin) vs. combination therapy.*

On the Horizon

FH treatment is rapidly evolving. Several promising approaches are in development or clinical trials:

- **Gene editing approaches (VERVE-2 trial):** CRISPR or base editing to permanently modify LDLR or PCSK9 genes. Early results show sustained LDL-C reductions with a single treatment. Could transform FH management.

- **Longer-acting PCSK9 therapies:** Injectable PCSK9 inhibitors that work monthly or even every 3 months (compared to current 2-week biweekly dosing) to improve adherence.
- **Combination agents:** PCSK9 inhibitors combined with other mechanisms (e.g., CETP inhibitors, bempedoic acid) to achieve even greater LDL-C reduction.
- **Expanded access programs:** For severely affected patients (homozygous FH, PCSK9-refractory), newer agents like evinacumab and inclisiran may become more widely available.

Key Takeaways

- **FH affects 1 in 250–500 people; >90% are undiagnosed** — yet it's the most preventable genetic cause of MI
- **LDL-C ≥190 mg/dL triggers FH evaluation** — especially if family history of early ASCVD
- **Genetic testing is now Class I (B-NR)** — the 2026 guideline mandates it for suspected FH
- **Standard risk calculators are Class III: Harm in FH** — use FH-specific scores instead
- **Treatment is aggressive and tiered:** <100 (no ASCVD), <70 (risk factors), <55 (with ASCVD)
- **Statin + ezetimibe + PCSK9i is the standard 3-drug combination** — newer drugs like inclisiran and evinacumab for refractory cases
- **Cascade screening saves lives:** 50% of your siblings and children carry the mutation
- **Early aggressive treatment prevents decades of disease** — children identified early have dramatically lower lifetime MI risk

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Next Steps

- If LDL-C >190 or family hx of early MI: Ask your doctor, **"Could I have familial hypercholesterolemia?"**
- Request genetic testing for LDLR, APOB, and PCSK9 mutations
- If diagnosed with FH, get your LDL-C to goal (don't settle for "normal" targets)
- Ask about cascade screening for siblings and children
- For young patients with FH: discuss whether combination therapy (statin + ezetimibe + PCSK9i) is warranted

Learn more at **CardioAdvocate.com** or the **FH Foundation**

Related CardioAdvocate Content

- **Hiding in Plain Sight** — Full FH diagnostic and treatment deep dive
- **Atherogenic Triad** — The lipid phenotype beyond FH
- **Lipid Guidelines** — 2026 treatment algorithm for all cholesterol disorders
- **Risk Calculators** — Why PREVENT replaces PCE
- **Lp(a)** — When elevated Lp(a) co-exists with FH
