Familial hypercholesterolemia (FH) poses a “silent” threat to patients with the condition, putting them at great risk of a coronary event. This genetic disorder, in which one or more mutations cause extremely high low-density lipoprotein (LDL) cholesterol levels, goes undiagnosed in approximately 80% of patients who have it. As a result, men with FH have a >50% risk of coronary heart disease (CHD) by age 50 and women with FH have a 30% risk of CHD by age 60. Patients with FH face a much higher risk of dying from a coronary event than those in the general population. For example, women between the ages of 20 and 39 who have this disorder are 125 times more likely to die of a coronary event than those who don’t.

Unfortunately, FH can be difficult to diagnose. Some patients have physical findings, but these features can be subtle and easily missed. Typically, however, FH is diagnosed based on a patient’s cholesterol level and family history. By implementing screening and early treatment for FH, you may be able to initiate treatment that can temper the development of atherosclerosis and possibly extend a patient’s life.

Two forms of the disorder, although one is more common

There are 2 types of FH:

- **Heterozygous FH (HeFH)** occurs in about 1 in 300 to 500 people, which makes it more common than Down syndrome. More than a half a million people in the United States have HeFH.

- **Homozygous FH (HoFH)** is more serious than HeFH, and less common, affecting one in 1 million people. Homozygous carriers suffer from CHD much earlier than those with HeFH; some die within the first few years of life.

Regardless of whether an affected individual inherited FH from one or both parents, more than one thousand mutations are known to cause inadequate clearance of LDL from
One of the most common mutations is a defective LDL receptor gene. Other abnormalities are known to occur with the proprotein convertase subtilisin/kexin type 9 (PCSK9) and apolipoprotein B genes.9

**Start with screening**

Suspect FH in patients who have a family history of premature heart disease. Also consider the patient’s ethnic background. The prevalence of FH is as high as one in 100 among certain groups, including French Canadians, Christian Lebanese, and 3 populations in South Africa (Ashkenazi Jews, Dutch Afrikaners, and Asian Indians).10

When there is high suspicion of FH based on a patient’s family history or ethnicity, additional screening is warranted for any patient older than age 2.11 If a patient’s family history is incomplete (eg, adoption, single-parent family), a lower threshold for screening is appropriate.

**Lipid screening** includes measuring serum total, LDL, and high-density lipoprotein cholesterol in either fasting or non-fasting samples. The United States Preventive Services Task Force (USPSTF) offers gender-specific recommendations for lipid disorder screening in the general population. For men, universal screening is recommended starting at age 35, and screening for those at increased risk of CHD should start at age 20.12

For women, the USPSTF recommends lipid screening only for those over age 20 who are at increased risk for CHD; such screening is strongly recommended for high-risk women ages 45 and older. In light of the serious consequences associated with FH, the National Lipid Association recommends lipid screening for all adults starting at age 20 (TABLE 1).13

**What about kids?** The recommendations for lipid screening in children and ad-

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**TABLE 1**

**Screening for familial hypercholesterolemia: Recommendations from the National Lipid Association**

<table>
<thead>
<tr>
<th>Universal screening for elevated serum cholesterol is recommended. Suspect FH in untreated patients with the following fasting cholesterol levels:</th>
</tr>
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<tbody>
<tr>
<td>• Patients age ≥20: LDL ≥190 mg/dL or non-HDL ≥220 mg/dL</td>
</tr>
<tr>
<td>• Patients age &lt;20: LDL ≥160 mg/dL or non-HDL ≥190 mg/dL</td>
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</table>

For all patients with these cholesterol levels, assess for a family history of high cholesterol and heart disease in first-degree relatives

<table>
<thead>
<tr>
<th>Consider cholesterol screening beginning at age 2 for children with a family history of premature cardiovascular disease or elevated cholesterol. All patients should be screened by age 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strongly suspect FH (and obtain lipid measurements) in patients with:</td>
</tr>
<tr>
<td>• Tendon xanthomas at any age (most common in Achilles tendon and finger extensor tendons, but also can occur in patellar and triceps tendons)</td>
</tr>
<tr>
<td>• Tuberos xanthomas or xanthelasma in patients younger than age 20 to 25</td>
</tr>
<tr>
<td>• Arcus corneae in patients younger than age 45</td>
</tr>
</tbody>
</table>

Strongly consider a diagnosis of FH and obtain further family information in patients with the following LDL levels:

| ≥250 mg/dL in those age ≥30 |
| ≥220 mg/dL in those age 20 to 29 |
| ≥190 mg/dL in those age <20 |

FH, familial hypercholesterolemia; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
adolescents are mixed. Both the USPSTF and the American Academy of Family Physicians indicate that there is insufficient evidence to screen for lipid disorders in asymptomatic children and adolescents. However, in a set of recommendations based on expert opinion, the National Heart, Lung, and Blood Institute (NHLBI) suggests universal screening for younger patients with a non-fasting lipid profile once between ages 9 to 11 and again between ages 17 to 21. The American Academy of Pediatrics has adopted the NHLBI recommendations.

Use validated criteria to make the diagnosis

Include FH in your differential diagnosis when evaluating patients with very high LDL levels. However, rule out possible secondary causes of elevated LDL before rendering a conclusion. Hypothyroidism, nephrotic syndrome, diabetes, and liver disease are among the most common secondary causes of high LDL cholesterol.

Several validated criteria sets can be used to establish an FH diagnosis. No single criteria set is more valid or more widely adopted
around the world. All 3 of the most commonly used criteria sets take into account family history and a patient’s LDL level, and 2 of the 3 factor in physical findings (TABLE 2).[9]

**Physical exam findings** that suggest FH can be subtle (FIGURE). Tendon xanthomas are a thickening of the soft tissue as a result of infiltration by lipid-rich cells. They most commonly occur at the Achilles and metacarpal tendons, but can also be seen at the patellar and triceps tendons. Xanthomas may not be readily visible, so it’s important to run your fingers over these areas to detect nodularity or thickening. While the presence of a tendon xanthoma makes FH highly likely, they are present in less than half of patients with FH.[17]

Tuberous xanthomas or xanthelasmas are waxy-appearing growths that may look yellow or orange and appear to be pasted on the skin in areas around the face, commonly the eyelids. The presence of xanthelasmas in a patient younger than age 25 suggests FH.

Finally, arcus corneae is an opaque ring around the outer edge of the cornea. When this is seen in patients younger than age 45,
it’s suggestive of FH. If you note tendon xanthomas, xanthelasmas, or arcus corneae while examining any of your patients, be sure to order an LDL level if it hasn’t already been done.

Is genetic testing necessary?
The only way to make a definitive diagnosis of FH is to find a mutation in a gene known to affect LDL metabolism. However, because genetic testing is expensive—and because more than one thousand different genetic defects can contribute to FH—it’s not practical to test every patient. Furthermore, since an estimated 20% of the mutations that contribute to FH have not yet been clearly delineated, a “normal” result on a genetic test might be misleading. Therefore, the diagnosis of FH usually is a clinical one. After clinically diagnosing a patient with FH, it’s imperative to screen first-degree family members by measuring their LDL cholesterol levels.

Lifestyle changes, statins can ward off CHD
Lifestyle modifications (ie, improved diet and exercise) and statins are the treatments of choice for patients with FH. Before starting pharmacotherapy, patients should undergo 3 months of lifestyle modification to assess how well this approach improves their lipid levels, assuming the patient doesn’t have additional risk factors such as hypertension or tobacco use, in which case he or she might require immediate pharmacotherapy. Statins can be initiated simultaneously with lifestyle choices in patients with an LDL >190 mg/dL.

**Lifestyle modification.** Although FH is a genetic problem, patients should be encouraged to make healthy choices regarding diet and exercise. While the best choices may not get FH patients to their LDL goal, better choices may mean that patients can take fewer medications, or lower doses of them. Healthy lifestyle choices can also have other positive effects on cardiovascular risk (eg, lowering blood pressure).

Patients can’t be expected to navigate their food choices alone, and several visits with a dietician will likely be needed. It’s important to emphasize the family influence on diet and get the entire family involved with making healthy food choices.

In addition to addressing diet and exercise, be sure to encourage patients to abstain from tobacco and manage stress as part of their overall effort to reduce the likelihood of a cardiovascular event.

**Statins.** Early treatment of FH with statins can delay initial coronary events and prolong life. In a 12.5-year study of 2146 patients with FH, approximately 80% of patients treated with statins survived without experiencing CHD, compared to slightly less than 40% of those who were not treated with statins. Patients treated with statins had a 76% reduction in risk of CHD compared to those who didn’t receive statins. Even low doses of statins started early have been shown to help avoid myocardial infarction in adults with FH.

The goal of treatment for FH is to reduced LDL levels by 50%. In pediatric patients, treating to an LDL level of 130 mg/dL is an alternative goal. Because it’s challenging to achieve this goal with improved diet and exercise alone, treatment with a statin is often necessary.

Statins can be used in children as young as age 8, or even earlier in homozygous FH. While a physician might be hesitant to start a chronic medication in a young patient, research shows that earlier intervention results in additional years of life. To date, no significant adverse effects of statins in pediatric patients have been identified, and statins have not been shown to impair growth. Young female patients should be counseled about the adverse effects statins can have on a fetus if the patient becomes pregnant while taking the medication.

Navigating the waters of statin treatment
Musculoskeletal symptoms are the most common adverse effect reported by patients taking statins. A thorough assessment of a patient’s muscle complaints is necessary to avoid prematurely concluding that he or she cannot tolerate statins.

A study in which “statin-intolerant” patients were re-challenged found that more than 90% of patients could tolerate statins through the course of the one-year study and
that it was likely that the patients’ initial muscle complaints were not due to statin use. (To read more about potential adverse events of statins, see “Statin adverse effects: Sorting out the evidence,” J Fam Pract. 2014;63:497–506.)

If LDL levels in a patient with HeFH remain at or above 160 mg/dL, intensifying treatment by adding another lipid-lowering medication might be warranted. For patients with HoFH, in whom the condition is more quickly life-threatening, there are additional choices, including LDL apheresis and medications such as mipomersen and lomitapide. Both of these medications can cause hepatotoxicity, and are available only through a Risk Evaluation and Mitigation Strategy program, which means they can only be prescribed by certified physicians. PCSK9 inhibitors are in the pipeline and may one day help patients with HoFH by addressing one of the genetic causes of this disorder.

References

The goal of treatment for familial hypercholesterolemia is to reduce LDL levels by 50%.