Familial Hypercholesterolemia: Screening, Diagnosis, and Treatment

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Familial hypercholesterolemia, an autosomal dominant genetic disorder, is characterized by markedly increased low-density lipoprotein (LDL) cholesterol that causes premature arteriosclerotic cardiovascular disease (ASCVD). Homozygous familial hypercholesterolemia typically presents with pathognomonic physical findings such as xanthomas or a corneal arcus. In contrast, heterozygous familial hypercholesterolemia is not indicated by clinical findings and is typically not diagnosed until after an early-onset ASCVD event (younger than 50 years).[1]

The worldwide prevalence of heterozygous familial hypercholesterolemia is estimated to be 1 in 250 to 350, and ASCVD events can occur with this condition as young as 17 years in men and by 25 years of age in women.[2-4] Screening for and diagnosing familial hypercholesterolemia in childhood can lead to treatment with lifestyle changes and medication, reducing the serious vascular effects of this dyslipidemia.

In 2023, the U.S. Preventive Services Task Force reaffirmed its previous assessment that evidence is insufficient to assess the balance of benefits and harms of screening for lipid disorders in children and adolescents younger than 20 years.[5] The recommendation acknowledges the lack of evidence that screening improves long-term health outcomes; however, the decision not to screen may lead to missed opportunities for early diagnosis and preventive treatment that can reduce the morbidity and mortality from ASCVD events that can occur before 50 years of age.[6]

The U.S. Preventive Services Task Force states, "…clinicians are encouraged to use their judgment when deciding whether to screen for lipid disorders in children and adolescents."[5] What, then, is a pragmatic approach to balance the opportunity for early diagnosis with the possible harms of treatment?

The National Heart, Lung, and Blood Institute and American Academy of Pediatrics recommend universal screening for children 9 to 11 years of age as one approach.[6] Most clinicians do not follow this guidance because of confusion about the guidelines and concerns about treatment effectiveness.[7]

Family physicians are in an ideal position to bring nuanced, family-centered knowledge to these decisions. The National Institute for Health and Care Excellence (NICE) provides one such approach.[8] NICE advocates reviewing medical records to identify families with members older than 16 years who have LDL cholesterol greater than 190 mg per dL (4.92 mmol per L) and a family history of ASCVD clinical events in men younger than 55 years and women younger than 65 years. These family members are then screened for dyslipidemia and genetically tested for familial hypercholesterolemia if the screening shows adults with LDL cholesterol greater than 190 mg per dL or children with LDL cholesterol greater than 155 mg per dL (4.01 mmol per L).[9] The American Heart Association endorses screening patients between 9 and 11 years of age to permit early identification of familial hypercholesterolemia and secondary "cascade" screening of other family members when a patient with familial hypercholesterolemia is identified.[1]

A reasonable practice is to combine the NICE and American Heart Association approaches and order a lipid profile for all family members older than 9 years who have a first-degree relative with a premature ASCVD event or a relative receiving treatment for LDL cholesterol greater than 190 mg per dL. The Dutch Criteria for Familial Hypercholesterolemia is a validated tool to assist clinicians in screening decisions and diagnosis (https://www.mdcalc.com/calc/3818/dutch-criteria-familial-hypercholesterolemia-fh).

After patients with familial hypercholesterolemia are identified, family physicians should provide lifestyle guidance to optimize blood pressure, weight, diet, physical activity, and tobacco cessation. Unless the physician has expertise with pharmacologic management of children and adults with familial hypercholesterolemia, referral to a cardiologist or lipidologist specializing in prevention is prudent.

Several medications that markedly reduce LDL cholesterol are often combined. These include proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (e.g., inclisiran [available as brand name Leqvio], PCSK9 siRNA), microsomal triglyceride transfer protein inhibitors (lomitapide [available as brand name Juxtapid]), and angiopoietin-like protein 3 inhibitors [evinacumab [available as brand name Evkeeza]). Other agents in phase 3 trials (e.g., pelacarsen, PSCK9 vaccines, olezarsen) may soon be used in familial hypercholesterolemia management.[10]

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Family physicians have an opportunity to identify and care for patients at high risk of ASCVD due to heterozygous familial hypercholesterolemia before the onset of cardiovascular clinical events. The proven benefit of LDL cholesterol reduction in the primary prevention of cardiovascular morbidity and mortality in high-risk patients supports identification and treatment of all patients with familial hypercholesterolemia.[11] Customizing and incorporating the NICE and American Heart Association recommended approaches, as well as using the Dutch criteria, can identify patients with familial hypercholesterolemia so that potentially life-saving preventive interventions can be initiated.

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