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Gap Analysis and Needs Assessment on Familial Hypercholesterolemia

Familial hypercholesterolemia (FH) represents a group of genetic diseases due to inborn errors in lipid metabolism, most commonly due to mutations in the low-density lipoprotein receptor (*LDLR*) gene.[1] FH results in severely elevated serum total cholesterol, with concentrations ranging from 350 to 550 mg/dL in heterozygous FH and 650-1000 mg/dL in homozygous FH.[1] Although the homozygous form is rare, heterozygous FH is one of the most prevalent congenital metabolic defects, affecting one in 300-500 people, and this rate is even higher in certain populations.[1] There are some 620,000 patients living with FH in the United States alone.[1] Despite its relatively high prevalence, FH is underdiagnosed and undertreated until patients develop symptoms or severe health problems.[1,2]

Adverse sequelae of FH begin in childhood, with continuously elevated levels of low-density lipoprotein cholesterol (LDL-C) leading to early risk of severe atherosclerosis and cardiovascular disease (CVD), especially in homozygotes and in patients with risk factors for coronary heart disease (CHD).[1] Untreated FH patients have a risk of premature CHD 20-fold higher than in healthy populations.[1] When CHD risk was expressed in terms of lifetime LDL-C exposure, FH homozygotes reached the critical threshold at about age 15, FH heterozygotes at age 40, and healthy controls after age 60 (Figure 1).[3] [Figure 1 not included here] About 50% of men and 30% of women with FH will have a myocardial infarction (MI) before age 60, with high mortality risk.[4]

Adverse sequelae of FH may also include tendon xanthomas, tuberous xanthomas, xanthelasma, and arcus corneae.[1,5,6] Over the long term, LDL receptor dysfunction may be associated with Alzheimer's disease, as suggested in a study where patients with FH had a significantly higher risk of mild cognitive impairment than those without the disease (21% vs 3%).[7] FH increases the risk of peripheral arterial disease by 5- to 10-fold and increases carotid or femoral artery intima-medial thickness versus healthy subjects.[8] Given the high prevalence of cardiovascular events, FH is associated with high health care costs, so early screening should help facilitate early treatment and thereby prevent serious adverse events.[2]

To accomplish these objectives, however, clinicians need a better awareness of FH. According to [faculty name removed], "This is one of my fields—and yet I don't really know anything about it. I know the heterozygotes are a lot of the people with high cholesterols, but I don't even know what gene to test for… And I would guess that 95 percent of everyone else is in the same boat."

- **Practice Gap #1:** Clinicians are not appropriately screening at-risk patients for FH or referring them for cascade screening of family members.
- **Learning Objective #1:** Convey the importance of universal screening for FH in children and cascade lipid screening for relatives of FH patients.

Clinicians do not recognize how common FH is. According to [faculty name removed], "In the homozygous case, there's really definitive evidence of just how bad it is, because it's kids having heart attacks at one year of age when they're homozygous. And if they're heterozygous, it's much more prevalent than people realize." He adds, "I think there are some very compelling statistics around how often you find it among people under 60 having an MI. It's something like 1 in 20. So it's really not a rare problem." Yet the lack of awareness is evident in the fact that some 85% of FH patients are undiagnosed.[9]

FH meets the criteria of the World Health Organization for a disorder amenable to screening, being an important health problem with an early symptomatic stage, available screening procedures, adequately understood natural history, available treatments, and high cost-effectiveness of early detection.[10]

In its recently published guidelines (2011), the National Lipid Association (NLA) recommends universal screening for elevated serum cholesterol, review of relevant family history of CHD risk factors, and genetic testing when indicated.[1,5] FH is diagnosed with a combination of LDL-C and non–high-density lipoprotein cholesterol (non–HDL-C); cutoff values in adults are LDL-C ≥190 mg/dL or non–HDL-C ≥220 mg/dL; respective values in patients younger than 20 years are ≥160 mg/dL and ≥190 mg/dL.[5]

Lack of recognition and undertreatment of FH are particularly acute among children; estimates indicate that only 20% of pediatric cases are diagnosed and even fewer among this group are treated appropriately.[1,11] Better education is needed for clinicians, patients, and parents, as well as consistent monitoring to reduce cardiovascular risk.[1,11] Clinicians must actively solicit patients' family health history and track any changes over time.[6] Risk factors for heart disease are particularly important in the modern era of rapidly rising rates of obesity and diabetes in adults and children worldwide.[12,13] Advancing age, another trend in the US population, is a non-modifiable risk factor for CHD.[14]

Given the autosomal dominant inheritance of FH, children and siblings of FH patients have a 50% risk of disease,[9] highlighting the importance of family testing. Cascade screening is considered both efficient and cost-effective for diagnosing heterozygous FH and improving life span in close relatives of the FH patient.[1,5,14,15] Formal guidelines for cascade screening have not been available in the US until recently,[1] which highlights the need for clinician education. Cascade screening has been recommended in the UK as well, where guidelines recommend combined LDL-C and DNA testing.[16,17] In a Dutch study, DNA testing of family members followed by early statin treatment afforded newly diagnosed FH patients an extra 3.3 years of life, on average, at a cost of $8700 per life-year gained, while avoiding 26 MIs per 100 persons treated.[2]

Cascade screening is an important reason for referral of FH patients to lipid specialists. In fact, the UK guidelines advocate specialist referral for all FH patients,[17] regardless of the success of statin treatment, to ensure that cascade screening is performed.[4] Yet studies indicate that only 15% to 27% of patients with FH are being treated in lipid clinics.[9,11] The US guidelines recommend referral to a lipid specialist if patients do not respond to initial therapy or have a very high CHD risk.[18] Children in particular should be referred right after diagnosis so that a lipid specialist can initiate and monitor lipid-lowering treatment.[12]

- **Practice Gap #2:** Clinicians are not fully aware of the need for aggressive treatment of FH and the available options other than statins.
- **Learning Objective #2:** Explain the need for aggressive treatment and the emerging treatment options for FH.

FH must be treated more aggressively than similarly elevated cholesterol in patients without FH.[4] According to a recent commentary, this is "not because the atherogenic effect of high blood concentrations of LDL cholesterol is any different in familial hypercholesterolemia, but because people with familial hypercholesterolemia are exposed to very high concentrations of LDL cholesterol from birth…. By the time the heterozygous familial hypercholesterolemia sufferer enters early adulthood they will have accumulated ≥20 years of continuous atherogenic exposure and are at a hundred-fold greater risk of a heart attack than other young people. Patients with homozygous familial hypercholesterolemia… are at such high risk that they may not live beyond childhood into early adulthood."[4] Because of the very high risk in FH patients and the universal need for treatment, the NLA urges clinicians not to waste time with traditional CHD risk-scoring algorithms or noninvasive imaging tests for atherosclerosis.[19]

Pharmacologic treatments for FH are always initiated after a trial of lifestyle treatment.[14,19] According to US and UK guidelines, FH unresponsive to lifestyle measures is then treated with aggressive lipid lowering, with the aim of reducing LDL-C by at least 50% in adults.[1,17] Both children and adults require drug treatment when LDL-C is ≥190 mg/dL or non–HDL-C is ≥220 mg/dL.[19] Most statins are approved for children beginning at age 10.[12]

Statins and other lipid-lowering medications are considered safe, effective, and cost-effective. [1,15] Studies document their efficacy in decreasing CVD morbidity and mortality in a dose-response manner[20] and reducing MI risk approximately to the level of that in the general population.[21] Yet despite the availability of well-established therapies, FH is undertreated.[1] A study in the Netherlands found that only 26% of FH patients were prescribed statins.[11] In another study, physicians sometimes advised FH patients to discontinue cholesterol-lowering treatment or not to begin at all; even when therapy was used, cholesterol levels did not meet international goals.[22]

Patients with severe disease or additional CHD risk factors need more intensive treatment to an LDL-C of <100 mg/dL.[19] High-dose statins alone may not be sufficient; in these cases ezetimibe, niacin, a bile acid sequestrant, or triple therapy may be needed.[14,19] Unfortunately, women intending pregnancy must discontinue statins, ezetimibe, and niacin for the duration of pregnancy and lactation, and other treatments must be considered, such as colesevelam or LDL apheresis.[1]

Statins are primarily effective for heterozygous FH.[14] High-dose statins can lower LDL-C in a small percentage of patients with homozygous FH, either by increasing LDL receptor activity or inhibiting lipoprotein assembly.[14] However, homozygous FH is generally resistant to conventional lipid-lowering drugs.[14] In general, therefore, LDL apheresis is the standard treatment for homozygous cases, and is required for intractable heterozygous cases.[1,14] LDL apheresis is considered safe and effective; however, it is costly, time-consuming, inaccessible for some patients and poorly tolerated by others, and it must be repeated every 1 to 3 weeks.[12,14,23,24] Liver transplantation is a less optimal strategy because of lifelong immunosuppression.[12,14]

According to [faculty name removed], cardiologists are frustrated with current therapeutic options: "I think most of them are trying to get to an LDL of 70 and are bothered by patients who have coronary disease who haven't gotten there." Relatively few patients are reaching LDL-C goals,[25] and compliance with lifelong therapies in general is estimated at only 50%.[26] Lipid-lowering therapy can be complicated by adverse effects, intolerance of high doses, poor compliance due to cost or multidrug regimens, and even clinician unawareness of the possible adverse effects.[19,27] Research shows that lifestyle and medication compliance is a particular problem when treatments are preventive (rather than curative), have a long duration, and when patients lack symptoms, as in many cases of FH.[26] Some researchers believe that patient adherence has been sorely neglected as a medical problem, both during clinical follow-up and in research.[26]

The pathophysiology of FH is not limited to elevated LDL-C. Although most cases are due to *LDLR* defects, the genes for apolipoprotein B (*APOB*) and proprotein convertase subtilisin/kexin type 9 (*PCSK9*) are also involved.[1] Lipoprotein-a [Lp(a)] is also considered an independent CVD risk factor in FH.[14,19,28] Emerging drug therapies are using novel means to target atherogenic lipoproteins other than LDL-C. Mipomersen is an Apo-B synthesis inhibitor that prevents the assembly of both LDL and Lp(a), rather than merely increasing LDL-C clearance.[29] Randomized, placebo-controlled phase III trials in heterozygous FH have shown that mipomersen significantly reduced LDL-C and Lp(a) by 21% to 39% versus placebo when added to maximum lipid-lowering drugs.[24,30] Other emerging therapies for FH-associated dyslipidemia include PCSK9 antibodies, which are intended to disrupt the interaction of PCSK9 with the LDL receptor.[25,31] Although this class is still under development, PCSK9 inhibitors show promise, especially because of findings that statins tend to up-regulate PCSK9.[31] Inhibitors of microsomal triglyceride transfer protein (MTP) are intended to interfere with the hepatic assembly of lipoproteins, although safety concerns are a current issue.[25] Inhibitors of cholesteryl ester transfer protein (CETP) block the transfer of cholesteryl esters from HDL to Apo-B–containing particles and are still being studied.[25] Finally, gene therapy for homozygous FH is under development.[12]

According to [faculty name removed], cardiologists need to know about new treatment opportunities and will then have more incentive to refer patients to specialists. He explains, "Currently all we do is give a statin, and if they're statin-intolerant we send them to the lipid clinic…. But if what the lipid clinic can offer isn't that much more than what we are [offering]—what we currently do anyway—then why refer? But now if there are new options for treatment, then that's a real new reason to do this." If clinicians become better educated about new therapies, then the scenario for diagnosis and treatment will have changed: "It's not just give atorvastatin 80 [mg] and throw up your hands, but there's a new treatment and you've got to get these people identified."

- **Practice Gap #3:** Clinicians must follow practice guidelines for the appropriate screening, diagnosis, and management of FH.
- **Learning Objective #3:** Review the new NLA guidelines, as well as existing international recommendations, for the screening, diagnosis, and management of pediatric and adult FH.

Dr. X [faculty name removed] believes that cardiologists need a simple management pathway indicating who to send for genetic tests, what gene to test for, which families to test, how to use new treatments, and how to monitor response, while "bringing all the erudite stuff to the practical level."

Indeed, a small survey of cardiologists (n=40) performed in 2012 identified significant knowledge gaps. Despite claiming at least "some" familiarity with FH, 35% of respondents had never knowingly treated and 53% were not currently treating an FH patient, and 38% were not comfortable with their knowledge of early detection and family screening. A majority did not know basic facts: 73% did not know the incidence of FH and 65% could not identify the elevation in risk of premature CHD in FH patients. Fully 68% were not aware or "not sure" of US national guidelines for FH diagnosis and management, yet despite this, 70% said they would not refer an FH patient. These data speak to the importance of promoting new and existing guidelines for FH screening, diagnosis, and management.

A separate questionnaire of European GPs (n=523) in 2011 revealed similar knowledge deficits, yet 75% of them said they believe that GPs are the most appropriate health care providers for detection and family screening for FH; only 38% thought lipid specialists were more appropriate. In yet another contradiction, most physicians in the UK (85%) believe that more education is needed on FH.

The unfamiliarity with existing guidelines is surprising given the wealth of advice available on treating elevated cholesterol, if not FH per se. Although the NLA guidelines for FH are new,[1] recommendations for the screening, diagnosis, and treatment of adults and children with high cholesterol have been available for years from the National Cholesterol Education Program,[14] the American Heart Association (AHA),[32] the AHA and the American College of Cardiology,[33] the Canadian Cardiovascular Society,[34] the National Institute for Health and Clinical Excellence (NICE),[17] and the European Society of Cardiology,[35] among others.

Of course, the mere existence of guidelines does not ensure that clinicians are aware of them or follow their recommendations. A survey of clinicians in 2002 on the topic of post-MI treatment revealed that "Despite the publication and widespread dissemination of the NCEP guidelines, the secondary prevention of CHD through screening and treatment of hyperlipidemia continues to be an underused clinical approach…. Management of high blood cholesterol levels is suboptimal for both primary care physicians and cardiologists."[36] The authors concluded that "More emphasis needs to be placed on the active dissemination of national guidelines for cholesterol management."[36]

These comments could also apply to practice guidelines for FH. In addition to those of the NLA,[1] specific validated criteria for diagnosing FH are readily available; NICE recommends those of the Simon Broome Register Group,[37] and other criteria have been published by the Dutch Lipid Clinic Network.[21] Finally, a US nonprofit organization called MEDPED is dedicated to promulgating information about inherited cholesterol disorders including FH, and the name of the group says it all: MEDPED means Make Early Diagnosis to Prevent Early Deaths.[38]

[Reference list removed]