Reducing the Burden of Disease and Death from Familial Hypercholesterolemia: A Call to Action

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Short title: Knowles et al.: A Call to Action

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Abstract

Familial hypercholesterolemia (FH) is a genetic disease characterized by substantial elevations of low-density lipoprotein cholesterol, unrelated to diet or lifestyle. Untreated FH patients have 20 times the risk of developing coronary artery disease, compared to the general population. Estimates indicate that as many as 1 in 500 people of all ethnicities, and 1 in 250 people of Northern European descent, may have FH; nevertheless, the condition remains largely undiagnosed. In the United States alone, perhaps as little as 1% of FH patients have been diagnosed. Consequently, there are potentially millions of children and adults worldwide who are unaware that they have a life-threatening condition. In countries like the Netherlands, the United Kingdom, and Spain, cascade screening programs have led to dramatic improvements in FH case identification. Given that there are currently no systematic approaches in the United States to identify FH patients or affected relatives, the patient-centric non-profit FH Foundation convened a national FH Summit in 2013, where participants issued a “call to action” to healthcare providers, professional organizations, public health programs, patient advocacy groups, and FH experts, in order to bring greater attention to this potentially deadly, but (with proper diagnosis) eminently treatable, condition.

Familial hypercholesterolemia (FH) is a frequently undiagnosed genetic disease characterized by substantial elevations of low-density lipoprotein cholesterol (LDL-C)—elevations that begin even before birth.[1] If FH is not identified and aggressively treated at an early age, affected individuals have a 20-fold increased lifetime risk of coronary heart disease compared with the general population.[2] Untreated men have a 50% risk of a fatal or nonfatal coronary event by age 50, and untreated women have a 30% risk by age 60.[2,3-6] Recent data from the National Heart, Lung, and Blood Institute (NHLBI)-funded exome sequencing project[7] have confirmed results from earlier studies showing that FH accounts for approximately 5% (i.e., roughly 13,000) of all annual myocardial infarctions (MIs) in Americans younger than 60 years old.[8]

FH is a genetic disease that is more common than cystic fibrosis, Marfan syndrome, and Down syndrome, and affects at least 1 in 500 individuals worldwide.[2,9] Nevertheless, these prevalence figures may underestimate the burden of FH in the United States (U.S.), as recent genetic studies[1,10] indicate that FH may actually affect as many as 1 in 250 individuals of Northern European descent. Familial hypercholesterolemia is caused by loss-of-function mutations in the low-density lipoprotein receptor (*LDLR*) and apolipoprotein B (*APOB*) genes, and gain-of-function mutations in the proprotein convertase subtilisin/kexin type 9 (*PCSK9*) gene.[11-14] The condition is a "co-dominant" disorder, with homozygotes (prevalence of 1 in 150,000 to 1 million) much more severely affected than heterozygotes. While children and adult heterozygotes generally have untreated LDL-C levels >160 and 190 mg/dl, respectively,[1,14] untreated LDL-C levels in homozygotes are commonly >450 mg/dl.[15]

Based on these estimates, there are likely 600,000 to 1.2 million children and adults at high risk for preventable vascular events due to FH. Despite the high prevalence and potential health impact of FH, it is often not identified as the cause of high cholesterol levels or major

coronary events by primary care providers or cardiologists. Fewer than 10% (and maybe as few as 1%) of individuals with FH in the U.S. have been properly diagnosed,[1] although the exact degree of underdiagnosis in the U.S. is difficult to estimate, due to gaps in screening, recognition, and classification of FH.

The current state of underdiagnosis is partly due to incomplete adoption of existing cholesterol screening recommendations from the U.S. Preventive Services Task Force, which recommends cholesterol testing in all adults to start at age 35 in men, age 45 in women, or age 20 if there is a family history of heart disease. In a recent National Center for Health Statistics Data Brief,[16] the Centers for Disease Control and Prevention (CDC) reported that only approximately 70% of adults aged 20 years and older (67% of men and nearly 72% of women) had a cholesterol screening test in 2011–2012; this rate did not significantly change from tests performed in 2009–2010. Unfortunately, the frequency of testing appears to be no higher in children. Despite the 2011 recommendation from the NHLBI and the American Academy of Pediatrics (AAP)[17] that all children have cholesterol levels measured between age 9 and 11 (and even earlier for those at high risk), these guidelines are not widely applied.[18]

Even individuals who have been diagnosed with very high LDL-C levels are rarely diagnosed with FH. A Danish survey of an unselected community-based population (n=69,016) found that 1 in 137 Danes had probable or definite FH; of these, 33% had coronary artery disease, yet only 48% of those with FH were on cholesterol-lowering medications.[10] Although comprehensive data on FH in the U.S. are not yet available, the situation is likely to be similar (or worse). For example, in a retrospective review of 176,363 medical records from a multidisciplinary clinic, 596 patients with LDL >195 mg/dl were identified as having “possible,”

"probable," or "definite" FH based on the Dutch Lipid Clinic Network criteria; of these 596 patients, only three had a clinical diagnosis of FH.[19]

Progress in FH research has been hampered by the lack of a specific International Classification of Diseases, Ninth Revision (ICD-9) code that would "flag" FH patients once they have been identified (**Table**). Current ICD-9 codes for pure hypercholesterolemia are widely applied to non-FH patients, which leads to misclassification and diminished ability to identify and track FH patients through electronic medical records.

A formal "case definition" with demonstrated clinical validity is needed to identify those affected with FH who can benefit from the available interventions. Diagnostic criteria such as the Dutch Lipid Clinic Network, Simon Broome, and Make Early Diagnosis to Prevent Early Death (MEDPED) criteria are relatively complex to implement in routine clinical settings, as some factors considered in the criteria (e.g., detailed family history of coronary disease, xanthomas, or FH) are often unavailable or not routinely ascertained.[20]

Failure to diagnose FH is particularly unfortunate given the multiple guideline-based therapeutic approaches to lower LDL-C. With optimal treatment, an affected individual's risk of cardiovascular disease is similar to the general population.[31] Perhaps more importantly, a failure to diagnose FH and initiate family-based "cascade" screening, places other potentially affected family members at great risk for preventable cardiovascular disease. Death and disability due to underdiagnosis and undertreatment are responsible for thousands of deaths, as well as millions of expended healthcare dollars each year.[21,23-25,32]

Systematic nationwide programs in other countries such as the Netherlands,[33] the United Kingdom,[21,26,32] and Spain[34] have combined identification of FH cases with family-based cascade screening efforts (via lipid and/or genetic testing) and aggressive statin-based treatment

regimens, resulting in dramatic improvements in case identification with concomitant decreases in catastrophic events.[35] A highly diagnostically- and cost-effective program in the Netherlands identified approximately 25,000 FH patients by the year 2013, representing at least one-third of the anticipated FH patients in that country.[1,25,36]

There are currently no systematic approaches to the identification of FH patients or to cascade screening of their relatives in the U.S. In addition, our healthcare system lacks key structural elements to facilitate the collection of national longitudinal data to measure and track the clinical progress of diagnosed patients. Although there are few examples of organized FH screening programs in the U.S., much can be learned from the Coronary Artery Risk Detection in Appalachian Communities (CARDIAC) program, which was initiated in West Virginia more than 15 years ago. The CARDIAC program offers lipid screening to every fifth-grader in the state, as well as to the parents of these students.[37-39] So far, the program has identified 108 (0.2%) children with probable FH (LDL-C >190 mg/dL). Cascade screening of the affected children's parents and other close relatives is underway. From 1983–1999 a statewide program in Utah used family history information to identify families at high risk of chronic diseases (including heart disease caused by FH) based on the pioneering work of the late Dr. Roger Williams. Although this program identified a large number of families at risk, it was not sustained due to lack of funding.[40] Some other state health departments have become involved in policy and surveillance related to FH. For example, in response to the 2011 AAP guidelines, the state of Michigan drafted a new Medicaid policy mandating dyslipidemia screening of covered children ages 9 to 11 years. The CDC's Behavioral Risk Factor Surveillance System (BRFSS) has been collecting data on health-related behaviors and chronic disease since 1984. Recently,

Connecticut added questions concerning family history of early MI and whether a health professional had ever discussed FH to their BRFSS state module.

The lack of progress in FH screening contrasts with the success of overall public health efforts in the U.S., which have resulted in significant reductions in heart disease risk and mortality by targeting the population at large with campaigns to decrease smoking and treat modifiable cardiovascular risk factors.[41] Undoubtedly, these larger-scale efforts have benefited FH patients, yet there remains a significant burden of preventable cardiovascular disease—particularly in those younger than 60 years of age in whom FH is a significant, but under-recognized, factor. Current FH diagnosis patterns and cascade screening of relatives are not optimal.[1] Increasing the ability of the U.S. to address FH screening and diagnosis will require collaborative action on multiple fronts.[1]

The FH Foundation is a patient-centric non-profit organization sought to catalyze collaborative diagnostic efforts through the inaugural Familial Hypercholesterolemia Summit: Awareness to Action (September 2013, Annapolis, MD). The FH Summit[35] convened scientists, clinicians, public health providers, and advocates to consider extant knowledge and implementation gaps in order to suggest strategies to confront these challenges. Stakeholders identified key action items to improve the identification of FH patients, trigger appropriate cascade screening of family members, track adherence to guideline-based therapeutic recommendations, and educate the public and health care providers on this under-recognized disorder (**Table**). The Summit participants identified the need for national surveillance indicators to be developed and applied in nationally representative population datasets in order to consider development of a new Healthy People 2020 (HP2020)[42] genomics goal on FH. In the meantime, the Summit recommended that all surveillance activities be aligned with the current HP2020

objectives related to cardiovascular disease.[42] These efforts dovetail with the recent American Heart Association (AHA)/American College of Cardiology (ACC) Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults,[22] which distinguishes adults with an LDL-C ≥190 mg/dL as being much more likely to have a genetically determined form of high cholesterol such as FH. Furthermore, this AHA/ACC guideline outlines specific recommendations for treatment of these individuals, as well as screening of their family members.

Given the evidence, the Summit participants issued a "call to action" that healthcare providers, professional organizations, public health programs, patient advocacy groups, and FH experts work together to bring greater attention to this eminently treatable condition. Addressing FH through the coordinated work of a variety of stakeholders, while simultaneously recognizing the public health and clinical medicine opportunities and challenges, will potentially cause a positive health impact on individuals in the U.S.

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Table. Proposed actions to address gaps and improve awareness, identification, and treatment of FH in the U.S.

Current gaps	Proposed actions
Case definition: There are several diagnostic algorithms[20] with partly overlapping criteria. Existing diagnostic criteria are not optimized to facilitate searches of electronic medical records or conducting epidemiological research.	Creation and adoption of a simplified case definition (in addition to formal diagnostic criteria) to help identify potential FH patients, thereby triggering appropriate work-up and treatment. Ideally this case definition would allow screening of electronic health records to identify potential FH patients.
Evidence-based guidelines: Such guidelines do exist but have not been widely adopted in the US.	Development and widespread adoption of evidence-based guidelines, such as those issued by the NICE in Great Britain in 2008,[21] the National Lipid Association[2] and the 2013 AHA/ACC lipid guidelines[22] in the US.
Cascade screening: There is no systematic approach to family-based cascade screening despite high level of evidence that this is life-saving and cost effective.[23-28]	Facilitation of evidence-based cascade screening of FH-affected families[29] and creation of policies that support availability and uptake. Because FH is autosomal co-dominant, all first degree relatives of heterozygous FH patients have a 50% chance of also having FH, making family screening imperative.
ICD-10 code: Existing (ICD-9) codes for dyslipidemia (such as code 272.0) are not specific for FH and are usually applied to individuals with "garden variety" LDL-C elevations. This hampers identification of FH patients and delivery of specific therapeutic recommendations	Establishment of an ICD-10 code that would be specifically applied to FH. This will allow optimal treatment of individuals with FH, help with screening of family members and increase the ability to "track" FH patients through electronic health record searches based on ICD-10 codes.
FH Patient Registry: Lack of an actively enrolling patient registry has impeded the ability to collect contemporary data on FH in the US. The MEDPED Registry[30] has not actively enrolled	Implementation and expansion of a representative patient registry for tracking and research. NOTE: The FH Foundation recently launched the CASCADE-FH Registry™ to fill this void.[29] There are two portals so that patients and healthcare

patients since 2004.	providers can enter relevant clinical data. This national, multi-center initiative will identify American FH patients, track their treatment regimens, and collect and report information on health outcomes over time.
Surveillance indicators: There are currently no national or state-based surveillance indicators for assessing needs or tracking progress in FH.	Gather data necessary to develop national and state-based surveillance indicators that can be tracked in population-based surveillance in order to align activities with HP2020 Heart Disease and Stroke objectives.
Training: There is a lack of understanding and awareness about FH among clinicians and public health providers.	Widespread training of healthcare and public health providers at all levels to heighten awareness about primary and secondary preventive strategies

ACC, American College of Cardiology; *AHA*, American Heart Association; *CASCADE-FH*, Cascade Screening for Awareness and Detection of Familial Hypercholesterolemia; *HP2020*, Healthy People 2020; *ICD-9*, International Classification of Diseases, Ninth Revision; *LDL-C*, low-density lipoprotein cholesterol; *MEDPED*, Make Early Diagnosis to Prevent Early Death; *NICE*, National Institute for Health and Clinical Excellence; *U.S.* United States