Reducing the burden of disease and death from familial hypercholesterolemia: A call to action

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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 with 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 nonprofit FH Foundation convened a national FH Summit in 2013, where participants issued a "call to action" to health care 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. (Am Heart J 2014;168:807-11.)

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 years, and untreated women have a 30% risk by age 60 years.[2-6] Recent data from the National Heart, Lung, and Blood Institute–funded exome sequencing project[7] have confirmed results from earlier studies showing that FH accounts for approximately 5% (ie, roughly 13 000) of all annual myocardial infarctions in Americans younger than 60 years.[8]

Familial hypercholesterolemia 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, 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 LDL 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. Although 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 United States have been properly diagnosed,[1] although the exact degree of underdiagnosis in the United States 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 US Preventive Services Task Force, which recommends cholesterol testing in all adults

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to start at age 35 years in men, age 45 years in women, or age 20 years 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 reported that only approximately 70% of adults 20 years and older (67% of men and nearly 72% of women) had a cholesterol screening test in 2011 to 2012; this rate did not significantly change from tests performed in 2009 to 2010. Unfortunately, the frequency of testing appears to be no higher in children. Despite the 2011 recommendation from the National Heart, Lung, and Blood Institute and the American Academy of Pediatrics[17] that all children have cholesterol levels measured between age 9 and 11 years (and even earlier for those at high risk), these guidelines are not widely applied.[18]

Even individuals who have been diagnosed as having very high LDL-C levels are rarely diagnosed as having 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 United States 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 3 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 are relatively complex to implement in routine clinical settings, as some factors considered in the criteria (eg, 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.[21] 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 health care dollars each year.[22-26]

Systematic nationwide programs in other countries such as the Netherlands,[27] the United Kingdom,[22,26,28] and Spain[29] 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.[30] 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.[1,25,31]

There are currently no systematic approaches to the identification of FH patients or to cascade screening of their relatives in the United States. In addition, our health care 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 United States, much can be learned from the Coronary Artery Risk Detection in Appalachian Communities program, which was initiated in West Virginia more than 15 years ago. The Coronary Artery Risk Detection in Appalachian Communities program offers lipid screening to every fifth grader in the state, as well as to the parents of these students.[32-34] 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 to 1999, a statewide program in Utah used family history information to identify families at high risk for 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.[35] Some other state health departments have become involved in policy and surveillance related to FH. For example, in response to the 2011 American Academy of Pediatrics guidelines, the state of Michigan drafted a new Medicaid policy mandating dyslipidemia screening of covered children aged 9 to 11 years. The Centers for Disease Control and Prevention's Behavioral Risk Factor Surveillance System has been collecting data on health-related behaviors and chronic disease since 1984. Recently, Connecticut added questions concerning family history of early myocardial infarction and whether a health professional had ever discussed FH to their Behavioral Risk Factor Surveillance System state module.

The lack of progress in FH screening contrasts with the success of overall public health efforts in the United States, which have resulted in significant reductions in heart disease risk and mortality by targeting the population at large with campaigns to decrease smoking

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

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 United States.	Development and widespread adoption of evidence-based guidelines, such as those issued by the NICE in Great Britain in 2008,[22] the National Lipid Association[2] and the 2013 AHA/ACC lipid guidelines[38] in the United States
Cascade screening: There is no systematic approach to family-based cascade screening despite high level of evidence that this is lifesaving and cost-effective.[23-25,28,39,40]	Facilitation of evidence-based cascade screening of FH-affected families[41] 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 for 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 United States. The MEDPED Registry[42] has not actively enrolled patients since 2004.	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.[41] There are 2 portals so that patients and health care providers can enter relevant clinical data. This national, multicenter 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 health care and public health providers at all levels to heighten awareness about primary and secondary preventive strategies

Abbreviations: *NICE*, National Institute for Health and Clinical Excellence; *MEDPED*, make Early Diagnosis to Prevent Early Death; *CASCADE-FH*, cascade Screening for Awareness and Detection of Familial Hypercholesterolemia.

and treat modifiable cardiovascular risk factors.[36] 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 in whom FH is a significant, but underrecognized, factor. Current FH diagnosis patterns and cascade screening of relatives are not optimal.[1] Increasing the ability of the United States to address FH screening and diagnosis will require collaborative action on multiple fronts.[1]

The FH Foundation is a patient-centric nonprofit organization sought to catalyze collaborative diagnostic efforts through the inaugural Familial Hypercholesterolemia Summit: Awareness to Action (September 2013, Annapolis, MD). The FH Summit[30] 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 underrecognized disorder (Table). The Summit participants identified the need for national surveillance indicators to be developed and applied in nationally representative population data sets in order to consider development of a new Healthy People 2020 (HP2020)[37] 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.[37] 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,[38] which distinguishes adults with an LDL-C $\geq$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 for these individuals, as well as screening of their family members.

Given the evidence, the Summit participants issued a "call to action" that health care 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 United States.

Disclosures

Dr Knowles, Dr O'Brien, Ms Greendale, Ms Wilemon, Dr Genest, Dr Sperling, and Dr Khoury have no relevant

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Dr Knowles had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Disclaimer

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References

1. Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J 2013;34:3478-3490a.
2. Goldberg AC, Hopkins PN, Toth PP, et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol 2011;5:S1-8.
3. Civeira F. Guidelines for the diagnosis and management of heterozygous familial hypercholesterolemia. Atherosclerosis 2004;173:55-68.
4. Reiner Z, Catapano AL, De Backer G, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J 2011;32: 1769-818.
5. Slack J. Risks of ischaemic heart-disease in familial hyperlipoproteinaemic states. Lancet 1969;2:1380-2.
6. Stone NJ, Levy RI, Fredrickson DS, et al. Coronary artery disease in 116 kindred with familial type II hyperlipoproteinemia. Circulation 1974;49:476-88.
7. Stitzel N, Do R, Hong-Hee W. Exome sequencing identifies rare alleles contributing to the inherited basis of early-onset myocardial infarction. Abstract presented at: American Heart Association Scientific Sessions; November 16-20, 2013; Dallas, TX. Circulation 2013;128:A14028.
8. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. Circulation 2013;127(1):e6-245.
9. Hopkins PN, Toth PP, Ballantyne CM, et al. Familial hypercholesterolemias: prevalence, genetics, diagnosis, and screening recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol 2011;5:S9-S17.
10. Benn M, Watts GF, Tybjaerg-Hansen A, et al. Familial hypercholesterolemia in the Danish general population: prevalence, coronary artery disease, and cholesterol-lowering medication. J Clin Endocrinol Metab 2012;97: 3956-64.
11. Austin MA, Hutter CM, Zimmern RL, et al. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. Am J Epidemiol 2004;160:407-20.
12. Hobbs HH, Russell DW, Brown MS, et al. The LDL receptor locus in familial hypercholesterolemia: mutational analysis of a membrane protein. Annu Rev Genet 1990;24:133-70.
13. Willer CJ, Schmidt EM, Sengupta S, et al. Discovery and refinement of loci associated with lipid levels. Nat Genet 2013;45:1274-83.
14. Youngblom E, Knowles JW. Familial hypercholesterolemia. In: Pagon RA, Adam MP, Ardinger HH, et al, eds. Genereviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2014.
15. Raal FJ, Santos RD. Homozygous familial hypercholesterolemia: current perspectives on diagnosis and treatment. Atherosclerosis 2012;223:262-8.
16. Carroll MD, Kit BK, Lacher DA, et al. Total and high-density lipoprotein cholesterol in adults: National Health and Nutrition Examination Survey, 2011-2012. NCHS Data Brief 2013;132:1-8.
17. No authorsExpert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics 2011;128:S213-56.
18. Dixon DB, Kornblum AP, Steffen LM, et al. Implementation of lipid screening guidelines in children by primary pediatric providers. J Pediatr 2014;164:572-6.
19. Gonzalez Santos L, Underberg J. Electronic chart review of a multispecialty internal medicine practice evaluating appropriate identification of patients with familial hyperlipidemia. J Clin Lipidol 2012;5:229.
20. Haase A, Goldberg AC. Identification of people with heterozygous familial hypercholesterolemia. Curr Opin Lipidol 2012;23:282-9.
21. Versmissen J, Oosterveer DM, Yazdanpanah M, et al. Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. BMJ 2008;337:a2423.
22. Wierzbicki AS, Humphries SE, Minhas R. Familial hypercholesterolaemia: summary of NICE guidance. BMJ 2008;337:a1095.
23. Alonso R, de Bobadilla JF, Méndez I, et al. Cost-effectiveness of managing familial hypercholesterolemia using atorvastatin-based preventive therapy. Rev Esp Cardiol (Engl Ed) 2008;61:382-93.
24. Nherera L, Marks D, Minhas R, et al. Probabilistic cost-effectiveness analysis of cascade screening for familial hypercholesterolaemia using alternative diagnostic and identification strategies. Heart 2011;97:1175-81.
25. Wonderling D, Umans-Eckenhausen MA, Marks D, et al. Cost-effectiveness analysis of the genetic screening program for familial hypercholesterolemia in the Netherlands. Semin Vasc Med 2004;4: 97-104.
26. DeMott K, Nherera L, Shaw EJ, et al. Clinical guidelines and evidence review for familial hypercholesterolemia: the identification and management of adults and children with familial hypercholesterolemia. London: National Collaborating Centre for Primary Care and Royal College of General Practitioners. 2008. [National Institute for Health and Care Excellence web site. http://www.nice.org.uk/guidance/cg71/resources/cg71-familial-hypercholesterolaemia-full-guideline3. Updated August 2008. Accessed July 2014].
27. Umans-Eckenhausen MA, Defesche JC, Sijbrands EJ, et al. Review of first 5 years of screening for familial hypercholesterolaemia in the Netherlands. Lancet 2001;357:165-8.

28. Hadfield SG, Horara S, Starr BJ, et al. Family tracing to identify patients with familial hypercholesterolaemia: the second audit of the Department of Health Familial Hypercholesterolaemia Cascade Testing Project. Ann Clin Biochem 2009;46:24-32.
29. Pocovi M, Civeira F, Alonso R, et al. Familial hypercholesterolemia in Spain: case-finding program, clinical and genetic aspects. Semin Vasc Med 2004;4:67-74.
30. Kindt I, O'Brien EC, Marquess M, et al. Proceedings of the FH Foundation's inaugural Familial Hypercholesterolemia Summit: Awareness to Action; September 18-19, 2013; Annapolis, MD; 2013.. [The FH Foundation web site. http://thefhfoundation.org/media/FH-Summit-2013-Proceedings-Final-clean-March-14th.pdf. Updated September 2013. Accessed July 2014].
31. Sjouke B, Kusters DM, Kindt I, et al. Homozygous autosomal dominant hypercholesterolaemia in the Netherlands: prevalence, genotype-phenotype relationship, and clinical outcome. Eur Heart J 2014. http://dx.doi.org/10.1093/eurheartj/ehu058.
32. No authors listedStatewide screening of fifth graders leads to identification and treatment of those with genetic predisposition to early-onset heart disease. AHRQ Health Care Innovations Exchange: Innovations and Tools to Improve Quality and Reduce Disparities web site. 2014. [http://www.innovations.ahrq.gov/content.aspx?id=3002. Updated January 15, 2014. Accessed July 7, 2014].
33. Cottrell L, John C, Murphy E, et al. Individual-, family-, community-, and policy-level impact of a school-based cardiovascular risk detection screening program for children in underserved, rural areas: the CARDIAC Project. J Obes 2013;2013:732579.
34. Ritchie SK, Murphy EC, Ice C, et al. Universal versus targeted blood cholesterol screening among youth: the CARDIAC project. Pediatrics 2010;126:260-5.
35. Johnson J, Giles RT, Larsen L, et al. Utah's Family High Risk Program: bridging the gap between genomics and public health. Prev Chronic Dis 2005;2(2):A24.
36. Centers for Disease Control and Prevention (CDC). Vital signs: avoidable deaths from heart disease, stroke and hypertensive disease—United States 2001-2010. MMWR Morb Mortal Wkly Rep 2013;62:721-7.
37. Healthy People 2020 web site. HealthyPeople.gov. Updated June 30, 2014. Accessed July 7, 2014.
38. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:S1-S45.
39. Ademi Z, Watts GF, Juniper A, et al. A systematic review of economic evaluations of the detection and treatment of familial hypercholesterolemia. Int J Cardiol 2013;167:2391-6.
40. Marks D, Wonderling D, Thorogood M, et al. Cost effectiveness analysis of different approaches of screening for familial hypercholesterolaemia. BMJ 2002;324:1303.
41. Ned RM, Sijbrands EJ. Cascade screening for familial hypercholesterolemia (FH). PLoS Curr 2011;3. [RRN1238].
42. Stephenson SH, Larrinaga-Shum S, Hopkins PN. Benefits of the MEDPED treatment support program for patients with familial hypercholesterolemia. J Clin Lipidol 2009;3:94-100.