AMERICAN COLLEGE of CARDIOLOGY

The Rationale and Design of the CASCADE FH Registry | Expert Analysis

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Introduction

Familial hypercholesterolemia (FH) is a genetic disease of elevated low-density lipoprotein cholesterol (LDL-C) that affects over one million people in the U.S.[1] Left untreated, FH results in a 20-fold increase in the lifetime risk of premature coronary heart disease due to high LDL-C exposure from birth.[2,3] It is currently estimated that FH is responsible for 2-5% of all myocardial infarctions in patients under the age of 60 years.[4,5] Unfortunately, it is estimated that fewer than 10% of FH patients are aware of their condition, many not until after an acute cardiovascular event has occurred.[6,7]

The Centers for Disease Control and Prevention has designated FH as a Tier 1 Genomics Application[8] due to its significant health burden on a largely undiagnosed FH population and the fact that with early diagnosis and treatment, cardiovascular risk is reduced to that of the general population.[9,10] In 2013, the CASCADE FH Registry was created by the FH Foundation, a patient-centered research and advocacy organization, to address this important public health problem.[11]

Snapshot in Time and a Way to Measure Progress

Extensive gaps in knowledge exist in the current landscape of FH treatment and cardiovascular disease burden in the U.S. Establishing a baseline of contemporary treatment patterns and cardiovascular risk profiles is an integral first step to begin tracking progress with FH over time as new knowledge and treatments emerge. Through CASCADE FH, the FH Foundation aims to increase awareness of this highly treatable condition among patients, providers, and their families to reduce

the risk of atherosclerotic disease. In addition, CASCADE FH will capture detailed information to fill existing knowledge gaps about current levels of LDL goal attainment, prevalence of CHD, and patient-reported outcomes in this population.[12]

The recent American College of Cardiology (ACC)/American Heart Association (AHA) 2013 and National Heart, Lung, and Blood Institute (NHLBI) Pediatric 2011 cholesterol treatment guidelines denote patients with LDL ≥190 (presumably FH) as a high-risk sub-group of patients who should be treated with high-intensity statin therapy.[13,14] FH is well-positioned to track adherence to and implementation of these guideline recommendations in routine clinical practice. By creating a network of patients, providers, and experts, the registry aims to answer important FH-specific clinical questions not answerable by current lipid research and optimize treatment to reduce the burden of cardiovascular disease. To be successful, the registry must enroll a sufficiently large number of patients to support its scientific objectives and produce evidence that is generalizable to the broader FH population.

Facilitating Case Identification

As an autosomal co-dominant disease, each first-degree relative of the index FH case has a 50% chance of being affected.[15] Therefore, an important objective of the CASCADE FH Registry is to promote case identification through family-based tracing, or cascade screening. There has been heightened interest in comparing cost-effectiveness of existing methods for identifying new cases to support this objective and whether optimal approaches incorporate universal screening, targeted/opportunistic screening, or some combination of these.

Whatever the method used to identify a proband, once that is accomplished, evidence from the scientific literature has consistently supported cascade screening as a cost-effective method for reducing morbidity.[16] Systematic national approaches to case identification and cascade screening have mostly been demonstrated after initial up-front investments of resources and infrastructure. Few systems in the U.S. have successfully implemented systematic approaches on a large-scale, despite a number of successful international initiatives.[17,18]

Integrating the registry with electronic health records (EHRs) may be a novel method to promote case identification and is the focus of FIND FH, a current initiative of the FH Foundation. The first step in this process is the selection of an

EHR phenotype for FH that can be defined using data collected as part of routine clinical care and are, thus, common to multiple EHR systems.[19]

As there is currently no diagnostic code (ICD-9 code) for FH, approaches that utilize orthogonal data including pre- and on-treatment lipid levels, prior history of cardiovascular disease, family history, medication use, physical exam findings are used to identify cases.[20,21] Some of these data require advanced methods such as natural language processing to access the wealth of information stored in an unstructured format in the EHR. Continual refinement and sharing of best practices across participating CASCADE FH sites will support future efforts that are nationally scalable and present a minimal cost burden to health care systems.

CASCADE FH Design Promotes Reduction of Disparities

A major challenge faced by national disease registries is enrolling a representative sample of patients and ensuring access for underserved populations. Recent studies suggest that African Americans and Mexican Americans are ~30% and 57% less likely than whites to have their cholesterol checked, respectively; minority patients are also less likely to reach treatment goals[22] and are underrepresented in clinical trials.[23] Enrollment of a geographically and racially diverse study population is fundamental to the registry's mission to reduce disparities in awareness and treatment.

The CASCADE FH Registry design is a hybrid design centered on two enrollment pathways: one through specialty lipid clinics and another through a patient web portal accessible to any interested FH patient across the country. While this hybrid design broadens access to the registry, additional barriers to participation in clinical research exist, including fear and mistrust, lack of education about the health consequences of FH, and concerns about privacy and confidentiality.[24,25] Prior work indicates that strong links to the community are integral to overcoming these barriers to engagement.[26,27] By leveraging existing community partnerships, the FH Foundation's outreach efforts hold promise to promote successful engagement of underrepresented populations.

FH Foundation Engages Patients as Part of the Solution

More data are needed on how well clinical decisions align with patient preferences and values. For example, the effects of emerging therapies on outcomes that matter to patients must be understood. Capture of patient-reported outcomes will complement knowledge on clinical outcomes from trials on novel lipid-lowering

therapies such as PCSK9 inhibitors.[28-31]

While FH research has historically been directed and driven by physician scientists, CASCADE FH is designed as a novel, patient-centric registry that empowers patients to be more engaged in their own condition, their community of fellow patients, the research about their disease, and ultimately as key participants for disseminating best care practices. As a patient-guided initiative, CASCADE FH is well-positioned to systematically capture and disseminate this information in a way that will support case identification through cascade screening, patient-centered treatment selection, and better cardiovascular outcomes for people with FH.

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Clinical Topics: **Arrhythmias and Clinical EP, Dyslipidemia, Prevention, Genetic Arrhythmic Conditions, Lipid Metabolism, Nonstatins, Novel Agents, Primary Hyperlipidemia, Statins**

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