Baseline Undertreatment of Adults with Newly Diagnosed Familial Hypercholesterolemia by Genomic Sequencing

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Abstract

BACKGROUND: Multiple sources suggest that the prevalence of Familial Hypercholesterolemia (FH) is approximately 1 in 200, with over 90% not formally diagnosed. Undiagnosed individuals may receive pharmacologic management for high cholesterol, but are likely undertreated for the condition. Geisinger Health System has enrolled patients in a large biobank project and is performing whole exome sequencing (WES) on all participants. Geisinger’s GenomeFIRST program identifies pathogenic changes consistent with FH and then re-engages patients for targeted care.

OBJECTIVE: Determine the pre- and post-WES diagnostic rate and optimal management of adults with pathogenic variants in one of the following genes: LDLR, APOB, or PCSK9.

METHODS: We conducted a retrospective analysis of electronic health record (EHR)-based information in a subgroup of patients with pathogenic variants in LDLR, APOB, or PCSK9 from a cohort of 60,726 WES patients. De-identified data was extracted from our centralized data warehouse on demographics, diagnoses, prescription profiles, and laboratory results. Patients were excluded if there were no reported LDL-C level within 5 years (N=93) or if deceased (N=6).

RESULTS: A total of 170 individuals met our inclusion criteria. Most patients (87%) had a previous diagnosis of hypercholesterolemia. Based on available EHR data, we estimate that 70% of patients met criteria for a clinical diagnosis of FH by the Dutch Lipid Diagnostic Criteria (i.e. met requirements for probable, possible or definite FH). Patients had a mean LDL-C level of 136 mg/dL (SD, 64, range 40 to 479 mg/dL) with half (N=91) reaching an LDL-C<100 mg/dL at least once. Majority (66%) of patients have previously received treatment with a high intensity statin and most (83%) have ever been prescribed a statin. Currently, 35% of patients are untreated with any lipid lowering agent and have a LDL-C mean of 142 mg/dL (SD, 59, range 60 to 383 mg/dL).

CONCLUSION: Over one third of patients were undiagnosed for FH prior to identification of a pathogenic variant. Further, the mean LDL-C was 36 mg/dL over goal and half never achieved recommended American Heart Association FH LDL-C goal of less than 100 mg/dL. Identifying patients with FH-associated variants through WES can enhance diagnostic recognition of FH and present clinicians with focused opportunities to more aggressively manage hyperlipidemia. The GenomeFIRST program to identify FH cases through genomic sequencing may serve as a model for improving both the diagnostic rate and optimal management for FH. Re-engagement of patients is planned to determine the positive predictive value of this diagnostic process.

Introduction

Familial Hypercholesterolemia (FH) is a life threatening genetic disorder marked by early onset of coronary artery disease (CAD) and stroke secondary to premature atherosclerosis resulting in significant lifetime elevations in low-density lipoprotein cholesterol (LDL-C) that is common but not uniformly recognized. While this condition affects over one million Americans, less than 1% are aware of their diagnosis. Recent work demonstrates FH patients with CAD are either undertreated or not treated for their condition.1,2

Methods

Setting

• Geisinger Health System: an integrated healthcare network in central and northeastern Pennsylvania.
• MyCode Community Health Initiative: a repository of blood DNA and serum samples from patients who consent to broad research use of their samples.
• GenomeFIRST: the return of medically actionable results to patients and their providers and integration into clinical care of patients.

Design

Retrospective analysis of electronic health record (EHR)-based information in a subgroup of patients with 35 pathogenic variants in LDLR, APOB, or PCSK9 from a cohort of 60,726 WES patients.

Inclusion criteria

• Enrolled in MyCode Community Health Initiative.
• Have 1 of 3 pathogenic variants in LDLR, APOB, or PCSK9.

Exclusion criteria

• No reported LDL-C level within 5 years (N=53).
• Deceased (N=6).

Statistical analysis

Descriptive summary statistics using means, standard deviations and ranges as appropriate.

Results

A total of 170 patients met criteria and were included in the study. This cohort was older (Median 61.5 years), majority female (61%) and almost all white (96%). A total of 41% of patients were untreated with any lipid lowering agent and had a LDL-C mean of 142 mg/dL (SD, 59, range 60 to 383 mg/dL).

CONCLUSION: Over one third of patients were undiagnosed for FH prior to identification of a pathogenic variant. Further, the mean LDL-C was 36 mg/dL over goal and half never achieved recommended American Heart Association FH LDL-C goal of less than 100 mg/dL. Identifying patients with FH-associated variants through WES can enhance diagnostic recognition of FH and present clinicians with focused opportunities to more aggressively manage hyperlipidemia. The GenomeFIRST program to identify FH cases through genomic sequencing may serve as a model for improving both the diagnostic rate and optimal management for FH. Re-engagement of patients is planned to determine the positive predictive value of this diagnostic process.

References


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