

Low-density Lipoprotein Cholesterol, Familial Hypercholesterolemia Mutation Status, and Risk for Coronary Artery Disease

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Background: The Utility of Genetic Testing in Severe Hypercholesterolemia (LDL \geq 190 mg/dl) is Uncertain

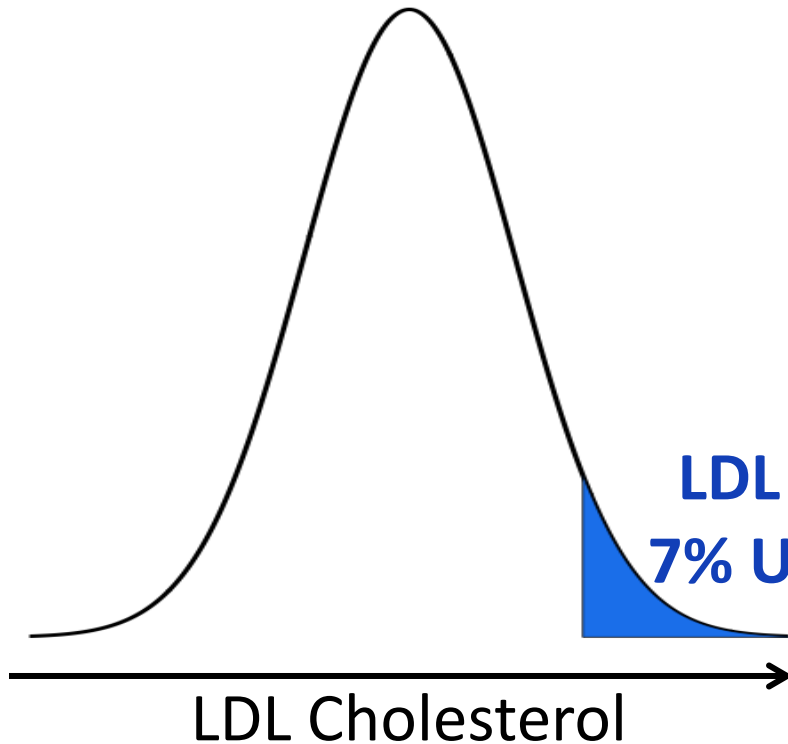
Study Objectives:

1. Diagnostic Yield

What proportion of individuals with LDL \geq 190 have a FH mutation?

2. Clinical Importance

For any given LDL, does coronary risk vary according to FH mutation status?



Monogenic (FH) —————→

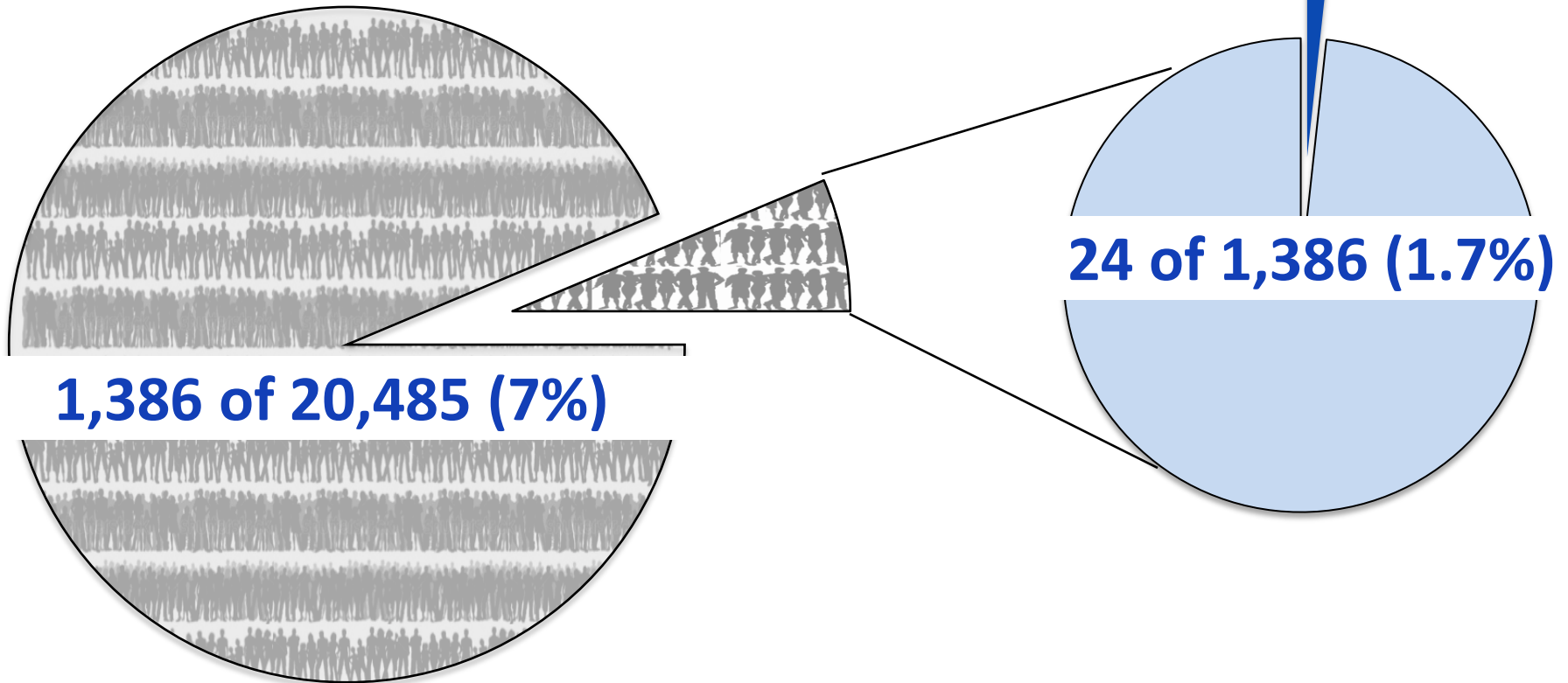
Polygenic —→—→—→—→—→

Environmental —————→

Diagnostic Yield: Fewer than 2% of Individuals with LDL \geq 190 mg/dl have an Identifiable FH Mutation

Severe Hypercholesterolemia
LDL Cholesterol \geq 190

FH Mutation Positive



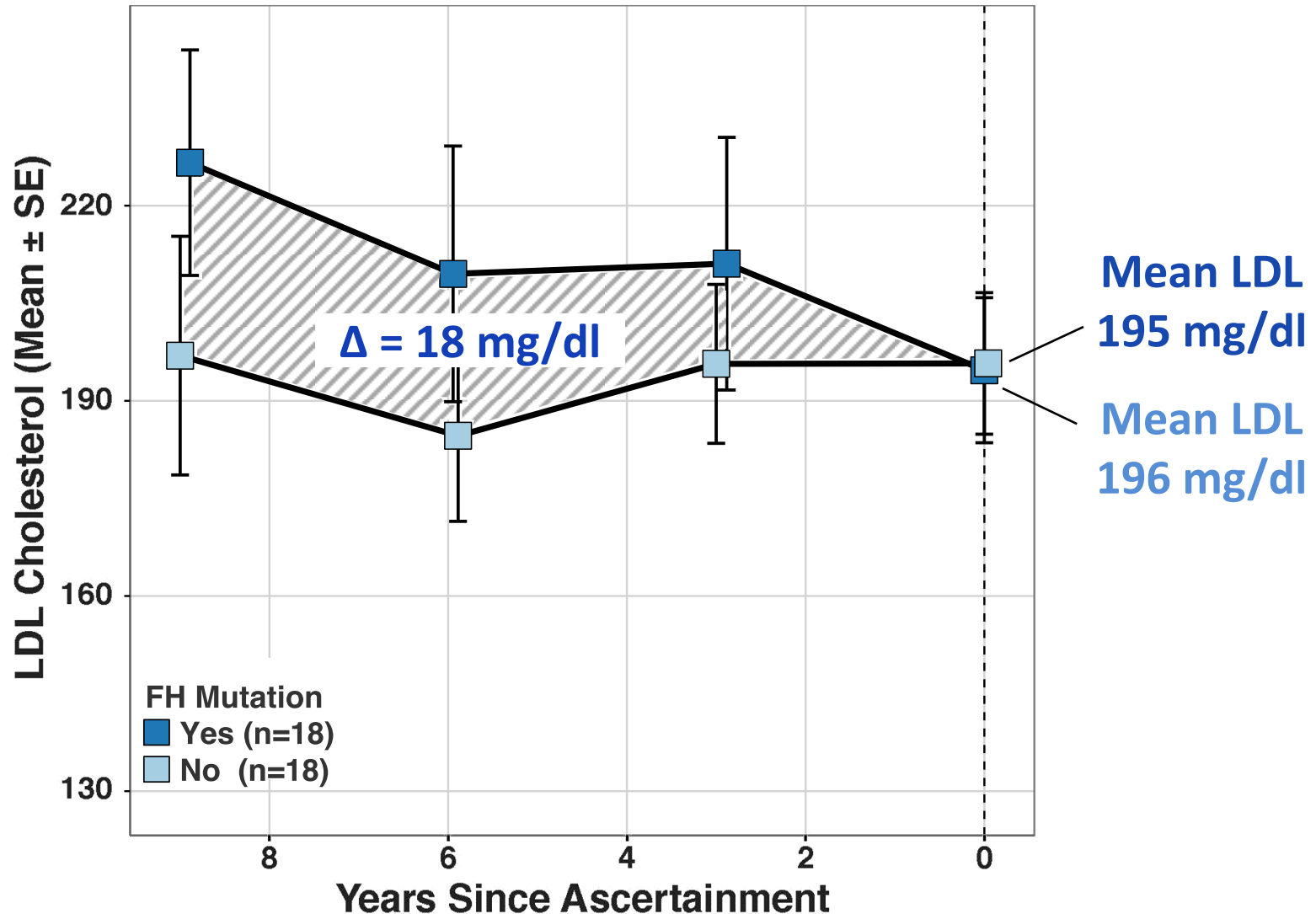
Clinical Importance: CAD Risk is Substantially Higher in FH Mutation Carriers with LDL \geq 190

	OR for CAD (95%CI)
LDL \geq 190 mg/dl	
FH Mutation (N = 1,264)	
FH Mutation (N = 73)	
LDL $<$ 130 & FH Mutation	Reference

Logistic Regression in Myocardial Infarction Genetics Consortium Studies

Covariates: Gender, Study, 5 principal components of ancestry

Potential Mechanism: FH Mutation Carriers have Higher Cumulative Exposure to LDL Cholesterol



Summary

1. Diagnostic Yield

Only about 2% of individuals with LDL \geq 190 have a FH mutation; remainder likely related to polygenic or environmental causes.

2. Clinical Importance

For any given LDL, risk of coronary artery disease is substantially higher among those with a FH mutation, likely due to increased lifelong exposure to circulating LDL.

**Additional Details Available in
Online Publication**



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