TESTING SET

Sample: 100 individuals (n=58 cases and 42 controls)

Defining cases and controls:
- A case status for familial hypercholesterolemia was assigned if the total score was >=6 points in individuals identified as a case for primary hypercholesterolemia
- A control status for familial hypercholesterolemia was assigned if the score was =<2 points in individuals identified as a case for primary hypercholesterolemia.

Statistics:
The positive predictive value (PPV) for being a case was determined as number of cases identified by the phenotyping algorithm and confirmed by review divided by the total number of cases identified by the algorithm.

The negative predictive value (NPV) for being a control was defined as number of true negatives in the numerator with total number of controls classified by the algorithm in the denominator.

Gold standard: manual chart review by an expert cardiologist-lipidologist initially blinded to a case-control status.

A subset of an algorithm-defined "unknowns" was included in the case group.

Sensitivity	98.3%
Specificity	100%
PPV	100%
NPV	97.7%

Iterative validation of performance of each step

Diagnostic accuracy of the individual components of the Mayo SEARCH algorithm v2.0 for ascertaining clinical criteria for FH (eMERGE cohort):

Variable	Sensitivity	Specificity	PPV	NPV
Xanthomas (n=100)	100	100	100	100
Family history of ASCVD (n=100)	98.4	100	100	97.3
Family history of hypercholesterolemia (n=100)	100	100	100	100
Premature CHD (n=100)	93.8	100	100	98.8
Premature CVD/PAD (n=100)	97.1	100	100	98.4

CHD=coronary heart disease; CVD=cerebrovascular disease; PAD=peripheral arterial disease

Diagnostic accuracy of the individual components of the Mayo SEARCH algorithm v1.0 for ascertaining FH criteria (ECH cohort):

Variable	Sensitivity	Specificity	PPV	NPV
Xanthomas (v3.0; n=60)	89	82	80	90
Corneal arcus ≤45 y (v2.0; n=40)	100	100	100	100
Family history of ASCVD (v2.0; n=120)	100	71	60	100
Family history of hypercholesterolemia (v1.0; n=20)	83	69	56	90
Premature CHD (v2.0; n=40)	100	83	80	100
Premature CVD (v 2.0; n=40)	100	77	70	100
Premature PAD (v2.0; n=40)	100	77	70	100