






ORIGINAL RESEARCH

# Estimated Yield of Screening for Heterozygous Familial Hypercholesterolemia With and Without Genetic Testing in US Adults

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**BACKGROUND:** Heterozygous familial hypercholesterolemia (FH) is a common genetic disorder causing premature cardiovascular disease. Despite this, there is no national screening program in the United States to identify individuals with FH or likely pathogenic FH genetic variants.

**METHODS AND RESULTS:** The clinical characteristics and FH variant status of 49 738 UK Biobank participants were used to develop a regression model to predict the probability of having any FH variants. The regression model and modified Dutch Lipid Clinic Network criteria were applied to 39 790 adult participants (aged  $\geq 20$  years) in the National Health and Nutrition Examination Survey to estimate the yield of FH screening programs using Dutch Lipid Clinic Network clinical criteria alone (excluding genetic variant status), genetic testing alone, or combining clinical criteria with genetic testing. The regression model accurately predicted FH variant status in UK Biobank participants (observed prevalence, 0.27%; predicted, 0.26%; area under the receiver-operator characteristic curve, 0.88). In the National Health and Nutrition Examination Survey, the estimated yield per 1000 individuals screened (95% CI) was 3.7 (3.0–4.6) FH cases with the Dutch Lipid Clinic Network clinical criteria alone, 3.8 (2.7–5.1) cases with genetic testing alone, and 6.6 (5.3–8.0) cases by combining clinical criteria with genetic testing. In young adults aged 20 to 39 years, using clinical criteria alone was estimated to yield 1.3 (95% CI, 0.6–2.5) FH cases per 1000 individuals screened, which was estimated to increase to 4.2 (95% CI, 2.6–6.4) FH cases when combining clinical criteria with genetic testing.

**CONCLUSIONS:** Screening for FH using a combination of clinical criteria with genetic testing may increase identification and the opportunity for early treatment of individuals with FH.

**Key Words:** cardiovascular disease ■ diagnostic screening ■ familial hypercholesterolemia ■ lipids

**H**eterozygous familial hypercholesterolemia (FH) is a common genetic disorder that causes elevated low-density lipoprotein cholesterol (LDL-C) and is associated with an increased risk of early-onset atherosclerotic cardiovascular disease (ASCVD).<sup>1,2</sup> An estimated 0.32% (95% CI, 0.26–0.39%) of individuals

worldwide, and 0.40% (95% CI, 0.32–0.48%) of US adults, have FH.<sup>1,3</sup> When untreated, the average age of first myocardial infarction in individuals with heterozygous FH is 50 years in men and 60 years in women, compared with 66 years in men and 72 years in women in the general population.<sup>4–6</sup> Early identification of FH

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## CLINICAL PERSPECTIVE

### What Is New?

- Individual clinical and genotype data from the UK Biobank were used to estimate the probability of any likely pathogenic familial hypercholesterolemia (FH) genetic variants.
- Dutch Lipid Clinic Network clinical criteria and the estimated probability of FH were applied to National Health and Nutrition Examination Survey participants to estimate the yield of FH screening in US adults.
- Clinical criteria-based screening alone could identify 3.7 FH cases per 1000 US adults screened, and adding genetic testing could increase this to 6.6 FH cases per 1000 adults screened.

### What Are the Clinical Implications?

- Combining clinical criteria with genetic testing could substantially increase the yield of screening for FH and identify >1 million US adults with FH.
- Screening for FH provides an opportunity for treatment to reduce the risk of cardiovascular disease in individuals with FH.
- Targeted FH screening strategies, such as genetic testing in young adults aged 20 to 39 years, may increase screening yield, and allow initiation of early preventive therapy.

## Nonstandard Abbreviations and Acronyms

<b>AHA</b>	American Heart Association
<b>DLCN</b>	Dutch Lipid Clinic Network
<b>FH</b>	familial hypercholesterolemia
<b>NHANES</b>	National Health and Nutrition Examination Survey

and initiation of lipid-lowering treatment can prevent early ASCVD events during the young adult and middle age years and reduce risk over a patient's lifetime.<sup>7,8</sup> The Centers for Disease Control and Prevention has thus identified FH screening as a tier 1 genomic application with public health benefits, yet current guidelines have conflicting recommendations for FH screening.<sup>9–12</sup>

FH may be identified using a combination of clinical (eg, abnormally elevated LDL-C and personal or family history of early ASCVD events) and genetic (ie, presence of likely pathogenic FH genetic variants) criteria, such as those used by Dutch Lipid Clinic Network (DLCN) or American Heart Association (AHA).<sup>3,4,13</sup> Although LDL-C screening in US adults is common, FH screening requires accurate collection of additional

clinical information or diagnostic genetic testing, which may be infrequent. In the CASCADE FH (Cascade Screening for Awareness and Detection of FH) patient registry, only 3.9% of patients with FH report genetic testing.<sup>14</sup> In the United States, national surveys do not collect data on FH variants, and the potential impact of genetic testing on the yield of national screening for FH has not been estimated. FH screening using clinical criteria, genetic testing, or in combination might help identify individuals with FH who would benefit from treatment to reduce the risk of premature ASCVD.<sup>15</sup>

We set out to estimate the probability of having any FH variants based on clinical characteristics and genotype data from participants in the UK Biobank. Then, we applied the UK Biobank–developed predictive model to US adults in the National Health and Nutrition Examination Survey (NHANES) to estimate FH screening yields based on clinical criteria alone using the modified DLCN clinical criteria, genetic testing alone, and combining clinical criteria with genetic testing.

## METHODS

All data used in this study are open access or publicly available. The analytic code used is available to interested researchers from the corresponding author on reasonable request.

### Study Population

#### UK Biobank

The UK Biobank is an open access resource that contains >500 000 participants aged 40 to 69 years from the United Kingdom between 2006 and 2010.<sup>16–18</sup> This analysis used data on all UK Biobank participants with whole exome sequencing data available. Each participant provided health history, medication lists, and family history of disease via questionnaires and interviews, and physical measures were obtained. All UK Biobank participants provided informed consent at time of enrollment. Analysis of UK Biobank data was approved by the Institutional Review Board at Mass General Brigham (Boston, MA).

#### National Health and Nutrition Examination Survey

NHANES is a cross-sectional national survey that collects demographic, questionnaire, and physical examination data on ≈5000 individuals in the United States every year. NHANES incorporates a complex multistage sampling design to estimate the prevalence of diseases in the United States. This analysis used pooled data from the 1999 to 2016 NHANES cycles and included participants aged ≥20 years. Individuals who were pregnant, had thyroid disease, had end-stage

kidney disease, were missing values for total cholesterol and high-density lipoprotein cholesterol (HDL-C), or had triglyceride level  $>800$  mg/dL (see Imputation of Missing NHANES Data below) were excluded. The Institutional Review Board at the National Center for Health Statistics of the Centers for Disease Control and Prevention approved the NHANES protocols, and all participants provided written informed consent.

### Variable Definitions

In both the UK Biobank and NHANES, self-reported values were used to define demographic variables (age, sex, and race), personal or family history of ASCVD events, age at time of ASCVD event, lipid-lowering treatment use, diagnosis of comorbidities (hypertension and diabetes), and smoking status (current, former, and never). A personal history of early ASCVD was defined as age of onset  $\leq 55$  years for men and  $\leq 60$  years for women.<sup>3</sup> In NHANES, we defined early family history of ASCVD using variables for a family history of early myocardial infarction or angina (ie, occurring before the age of 50 years) in a first-degree relative.<sup>3</sup> We used physical measures for systolic blood pressure, diastolic blood pressure, and body mass index, which were all assessed as continuous variables. In the UK Biobank, lipid values were obtained via direct measurement, including LDL-C concentration, which was measured using a Beckman Coulter assay. In NHANES, total cholesterol, HDL-C, and triglycerides are obtained via direct measurement. Fasting laboratory values for triglycerides were obtained for approximately half of NHANES participants, and LDL-C is calculated using the Friedewald equation for individuals with triglyceride level  $<400$  mg/dL.

### Imputation of Missing NHANES Data

In NHANES, multiple imputation was used for missing smoking status, height, weight, body mass index, systolic blood pressure, diastolic blood pressure, anti-hypertensive treatment, hypertension diagnosis, LDL-C, triglycerides, lipid-lowering treatment use, diabetes diagnosis, personal history of ASCVD, early ASCVD, and family history of early angina or myocardial infarction.<sup>3</sup> Multiple imputation by chained equations was used to generate 10 multiply imputed data sets (“mice” R package). Outside of triglycerides and LDL-C, missingness was  $<5\%$  per variable. Predictive mean matching was used to impute continuous variables, logistic regression to impute binary variables, and polytomous logistic regression to impute categorical variables. A sensitivity analysis was performed, restricting the sample to only individuals in NHANES with complete data on all variables.

Passive imputation was used to calculate LDL-C for all NHANES participants, replacing the Centers for

Disease Control and Prevention–reported Friedewald values with a recently published equation from Sampson et al.<sup>19</sup> The Sampson equation has more accurately calculated LDL-C than either the Friedewald or Martin-Hopkins equation by internal validation and compared with  $\beta$ -quantification and direct LDL-C, particularly when LDL-C is low or triglycerides are high (ie,  $>400$  and  $\leq 800$  mg/dL).<sup>19</sup> The effect of using the Martin-Hopkins and Friedewald equations was explored in sensitivity analyses. For participants using lipid-lowering treatment, the untreated LDL-C was estimated by multiplying their LDL-C by 1.43.<sup>3,13,20</sup>

### Familial Hypercholesterolemia

In the UK Biobank, likely pathogenic or pathogenic FH variants were identified by certified laboratory geneticists using clinical criteria for pathogenicity, as has previously been reported.<sup>17</sup> In NHANES, the presence of any genetic variants was probabilistically assigned to each participant based on logistic regressions from the UK Biobank (see Statistical Analysis section). Using modified DLCN criteria, NHANES participants were then assigned points based on their untreated LDL-C, personal history of early ASCVD, family history of early myocardial infarction or angina in a first-degree relative, and FH genetic variant (Table 1).<sup>3,13</sup> FH cases were defined as individuals with definite or probable FH (ie, DLCN  $\geq 6$  points).<sup>3,13</sup> In a secondary analysis, FH cases were identified using modified AHA criteria for FH if their untreated LDL-C was  $\geq 190$  mg/dL and they had a personal history of early ASCVD, family history of early myocardial infarction or angina in a first degree relative, or an FH genetic variant.<sup>4</sup>

### Statistical Analysis

In the UK Biobank, characteristics were compared between those with and without any FH variant using an ANOVA for continuous variables,  $\chi^2$  test for categorical variables, and the Kruskal-Wallis test for nonnormally distributed measurement variables. The likelihood of having any FH variant was estimated in the UK Biobank using multivariable logistic regression. On the basis of clinical judgement, age, sex, LDL-C, HDL-C, personal history of ASCVD, family history of early myocardial infarction or angina, and statin use were prespecified for inclusion in all models. Additional covariates considered for inclusion were triglycerides, race, body mass index, smoking status, diabetes, systolic blood pressure, diastolic blood pressure, untreated LDL-C, interaction between age and LDL-C, age squared, and variable transformations (eg, natural log and square root). The final model was selected as the most parsimonious that maximized the area under the receiver-operating characteristic curve. The model fit was further examined by comparing the observed

**Table 1. Heterozygous FH Definitions**

Classification	Clinical criteria alone	Genetic testing
Dutch Lipid Clinic Network <ul style="list-style-type: none"> <li>Definite or probable FH (≥6 points)</li> </ul>	<ul style="list-style-type: none"> <li>Untreated LDL-C <ul style="list-style-type: none"> <li>≥330 mg/dL: 8 points</li> <li>250–329 mg/dL: 5 points</li> <li>190–249 mg/dL: 3 points</li> <li>155–189 mg/dL: 1 point</li> <li>&lt;155 mg/dL: 0 points</li> </ul> </li> <li>Personal history of early ASCVD: 2 points</li> <li>Family history of early myocardial infarction or angina in a first-degree relative: 1 point</li> </ul>	<ul style="list-style-type: none"> <li>Any FH variant: 8 points</li> </ul>
American Heart Association	<ul style="list-style-type: none"> <li>Untreated LDL-C ≥190 mg/dL with <ul style="list-style-type: none"> <li>Personal history of early ASCVD or</li> <li>Family history in a first-degree relative of early myocardial infarction or angina</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Any FH variant</li> </ul>
Genetic testing alone	N/A	<ul style="list-style-type: none"> <li>Any FH variant</li> </ul>

ASCVD indicates atherosclerotic cardiovascular disease; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; and N/A, not applicable.

and predicted prevalence of FH variants by quintile of predicted prevalence.

The multivariable logistic regression model developed in the UK Biobank was then used to predict the probability of an FH variant in NHANES participants. For each participant, a uniform distribution ranging from 0 to 1 was randomly sampled. If the sampled value was less than or equal to their predicted probability of having an FH variant, the participant was assigned as having an FH variant. To incorporate uncertainty in assigning FH variant status, each participant was repeatedly assigned an FH variant status by resampling the uniform distribution (100 times) separately in each of the 10 multiply imputed data sets. The survey-weighted mean FH variant prevalence was estimated across all 100 iterations.

The number of FH cases that would be identified by screening programs if only clinical criteria were used (ie, modified DLCN or AHA criteria ignoring presence of FH variants), only genetic testing was used (ie, presence of any FH variant), and by combining clinical criteria with genetic testing. The FH screening yield (ie, number of FH cases identified per 1000 screened) for each strategy was estimated. The screening yield in subgroups of interest was also estimated: age groups (ie, 20–39, 40–59, and ≥60 years), observed LDL-C level regardless of current treatment status (ie, <130, 130–159, 160–189, and ≥190 mg/dL), 10-year ASCVD risk (ie, <7.5% and ≥7.5%) in adults aged ≥40 years, hypertension status, and lipid-lowering treatment status.

All analyses were performed using R (version 4.0.2; Vienna, Austria). All NHANES analyses accounted for the complex survey design (“survey” R package), and, for the multiply imputed analyses, results were pooled across all imputed data sets (“mitools” and “lodown” R packages).

## RESULTS

### Study Population

The mean (SD) baseline age of the 49 738 participants in the UK Biobank was 57.1 (8.0) years, 54.5% were women, and 93.4% were White race (Table 2). Compared with those without any FH variants (N=49 607), participants with any FH variants (N=131) had a higher LDL-C (mean, 159.9 versus 136.5 mg/dL;  $P<0.001$ ), higher estimated untreated LDL-C (mean, 198.0 versus 145.0 mg/dL;  $P<0.001$ ), higher total cholesterol (243.7 versus 219.5 mg/dL;  $P<0.001$ ), and higher use of lipid-lowering therapy (59.5% versus 19.5%;  $P<0.001$ ) (Table S1). In addition, more participants with any FH variants than without had a personal history of ASCVD (13.7% versus 4.8%;  $P<0.001$ ) and a family history of coronary heart disease (66.4% versus 46.0%;  $P<0.001$ ).

A total of 39 790 NHANES participants were included in the primary analysis in which missing data were imputed and 16 103 were included in the sensitivity analysis of those with complete data (Figure 1, Table 2, and Table S2). NHANES participants had a mean (SD) age of 46.4 (16.7) years, 48.6% were women, and 68.5% were White race. Mean (SD) estimated untreated LDL-C was 126.1 (40.1) mg/dL, mean (SD) total cholesterol was 196.6 (41.5) mg/dL, 7.4% had a personal history of ASCVD, and 11.9% had a family history of early coronary heart disease.

### Probability of Any FH Variants

The prevalence of any FH variants in the UK Biobank was 0.27%. The final multivariable regression model included age, sex, use of lipid-lowering therapy, LDL-C, HDL-C, triglycerides, personal history of ASCVD, and



**Table 2. Participant Characteristics**

Characteristics	UK Biobank	NHANES
Total No.	49 738	39 790
Demographic		
Age, y	57.1 (8.0)	46.4 (16.7)
Women	54.5	48.6
Race or ethnicity		
White	93.4	68.5
Black	2.0	11.0
Hispanic	...	14.0
Other†	4.6	6.5
Cholesterol		
LDL-C, mg/dL	136.6 (33.2)	119.7 (35.8)
Estimated untreated LDL-C, mg/dL	145.1 (32.8)	126.1 (40.1)
HDL-C, mg/dL	56.9 (14.9)	52.8 (16.2)
Triglycerides, mg/dL*	128.1 (90.9–183.6)	109.5 (75.8–161.8)
Total cholesterol, mg/dL	219.6 (43.9)	196.6 (41.5)
Use of any lipid-lowering therapy	19.6	13.4
Other clinical		
Body mass index, kg/m <sup>2</sup>	27.4 (4.8)	28.5 (6.6)
Hypertension	29.4	35.5
Systolic blood pressure, mm Hg	139.0 (19.0)	122.4 (17.6)
Diastolic blood pressure, mm Hg	82.0 (11.0)	71.5 (11.0)
Diabetes	5.9	8.2
Personal history of ASCVD	4.8	7.4
Family history/early family history of CHD†	46.1	11.9
Family history of stroke	28.4	...
Smoking status		
Never	55.4	53.2
Former	35.3	24.3
Current	9.0	22.6

The table shows the participant characteristics at the time of enrollment in UK Biobank. Participant characteristics are shown at the time of the NHANES examination and are shown for the total included sample in the primary analysis, for which missing data were multiply imputed. NHANES participant characteristics from the complete case analysis, in which there were only participants with complete data on needed variables, are shown in Table S1. Values are presented as mean (SD) and percentages. ASCVD indicates atherosclerotic cardiovascular disease; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and NHANES, National Health and Nutrition Examination Survey.

\*Triglycerides are reported as median (interquartile range).

†Family history of early CHD in NHANES.

‡Asian, American Indian/Alaskan Native, and Native Hawaiian/Pacific Islander.

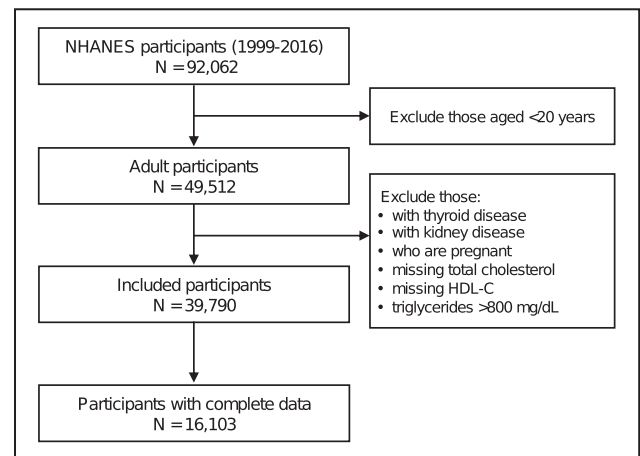
family history of early coronary heart disease (Table 3). The model accurately predicted the probability of having any FH variants with a predicted probability of any FH variants of 0.26% and an area under the receiver-operating characteristic curve of 0.88. The calibration plot by quintile of predicted probability is shown in Figure 2. In NHANES, the predicted probability (95%

CI) of any FH variants was 0.38% (0.33–0.42%) in the primary analysis and 0.37% (0.32–0.43%) in the sensitivity analysis of complete cases (Table S3). The probability of an FH variant increased with LDL-C, specifically 5.32% (95% CI, 4.10–6.77%) in those with an LDL-C ≥190 mg/dL and 4.04% (95% CI, 3.33–4.84%) in those with an estimated untreated LDL-C ≥190 mg/dL.

### FH Screening Yield

FH screening in US adults was estimated to identify 652 100 (523 200–803 000) cases using DLCN clinical criteria alone and 659 000 (478 600–885 800) using genetic testing alone (Figure 3, Table 4, and Table S4). An estimated 25.1% of FH cases identified using genetic testing would also meet DLCN clinical criteria alone, leading to 1 145 900 (931 100–1 395 400) FH cases identified with a combined strategy (ie, using clinical criteria with genetic testing). Per 1000 people screened, FH screening would yield 3.7 (3.0–4.6) cases using clinical criteria alone, 3.8 (2.7–5.1) using genetic testing alone, and 6.6 (5.3–8.0) using clinical criteria with genetic testing.

Screening yields for subgroups of interest are in Table 4 and Table S4. In young adults aged 20 to 39 years, DLCN clinical criteria alone were estimated to yield 1.3 (0.6–2.5) FH cases per 1000 individuals screened, which would increase to 4.2 (2.6–6.4) when combined with genetic testing. Using clinical criteria alone would yield 77.3 (57.7–101.0) FH cases per 1000 individuals screened in those with an observed LDL-C ≥190 mg/dL and 65.2 (52.6–79.7) in those with an estimated untreated LDL C ≥190 mg/dL. Adding genetic testing would further increase the estimated yield to 103.6 (78.1–133.9) in those with an LDL-C ≥190 mg/dL and 89.1 (71.9–109.0) in those with an estimated untreated LDL ≥190 mg/dL. Among individuals not



**Figure 1. National Health and Nutrition Examination Survey (NHANES) study population flowchart.**

The figure shows the number of NHANES participants included in the analysis after applying the inclusion and exclusion criteria. HDL-C indicates high-density lipoprotein cholesterol.

**Table 3. Likelihood of Any FH-Causative Genetic Variants in UK Biobank Participants**

Covariates	$\beta$ Coefficient	SE	P value
Intercept	-6.36	0.90	<0.001
Age at baseline	-0.04	0.01	0.003
Men	-0.58	0.21	0.007
Lipid-lowering treatment use	2.95	0.22	<0.001
LDL-C	0.04	0.00	<0.001
HDL-C	-0.04	0.01	<0.001
Triglycerides	-0.01	0.00	<0.001
Personal history of ASCVD	0.75	0.30	0.013
Family history of early CHD	0.58	0.20	0.004

The table shows the final multivariable logistic regression model predicting the probability of any FH-causative genetic variants in UK Biobank participants. The area under the receiver-operator characteristic curve was 0.877. ASCVD indicates atherosclerotic cardiovascular disease; CHD, coronary heart disease; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol.

using statins, clinical criteria combined with genetic testing was estimated to yield 2.9 (2.0–4.1) FH cases per 1000 individuals screened. Among those with a 10-year ASCVD risk <7.5% and  $\geq$ 7.5%, the screening yield using genetic testing alone was estimated to be

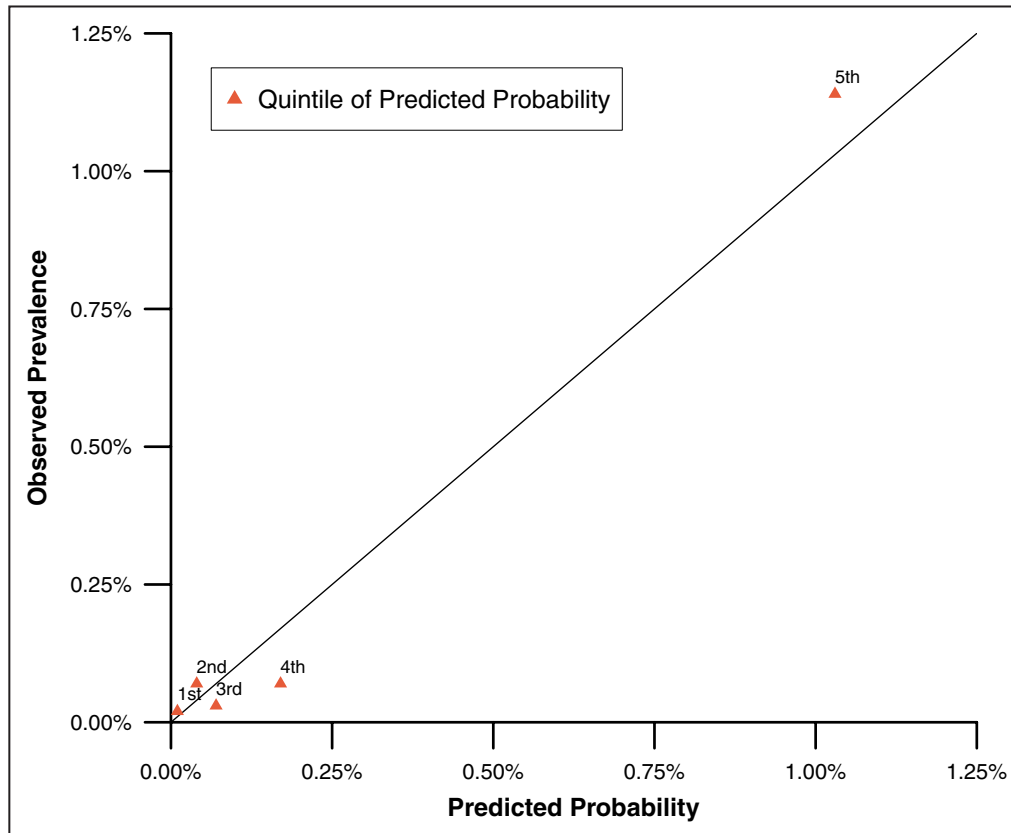
3.3 (1.7–5.7) and 4.9 (2.9–7.8), respectively, and with clinical criteria combined with genetic testing, 5.3 (3.4–8.0) and 11.6 (8.8–15.0), respectively.

### Sensitivity Analysis

In the complete case analysis, using DLCN clinical criteria with genetic testing would identify 1 021 000 (770 400–1 327 100) FH cases (Table S4). Using the AHA clinical criteria combined with genetic testing would increase the number of FH cases identified to 2 290 900 (1 889 400–2 778 300) and yield 13.1 (10.8–15.9) FH cases per 1000 individuals screened (Table S5). Using the Friedewald or Martin-Hopkins equations to calculate LDL-C instead of the Sampson equation did not substantially alter either the LDL-C or screening yield estimates with DLCN clinical criteria alone (Table S6).

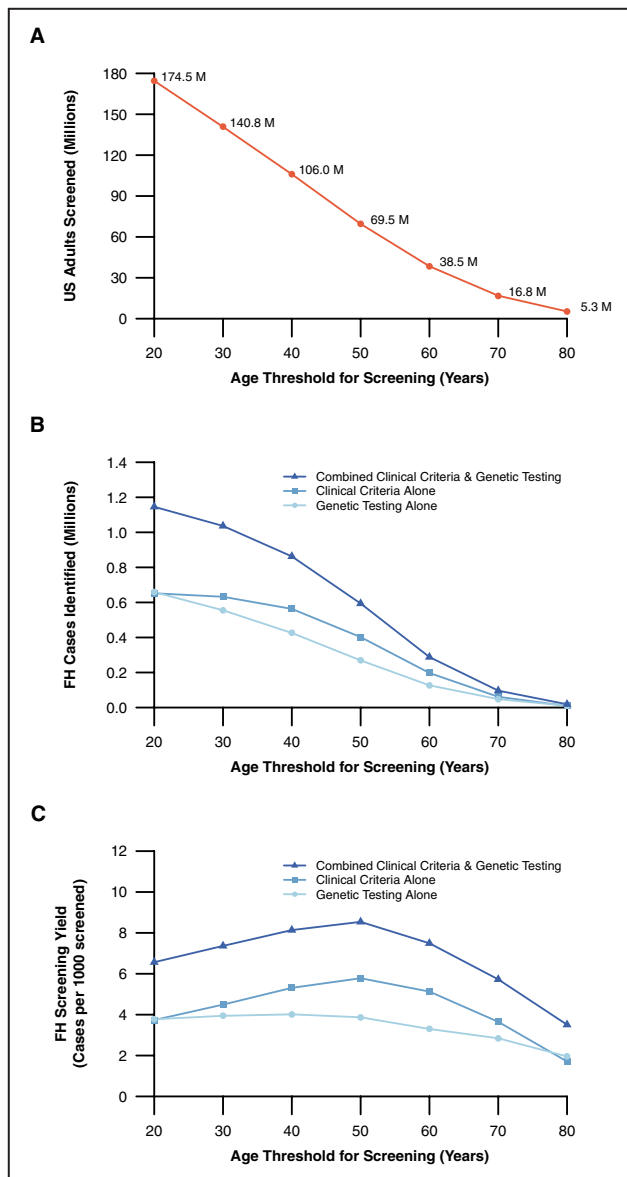
### DISCUSSION

In this analysis, we combined the strengths of UK Biobank whole exome data with US nationally representative NHANES survey data to estimate the diagnostic yield of screening for FH in US adults using clinical criteria and genetic testing. We estimated that



**Figure 2. Predicted probability vs observed prevalence of familial hypercholesterolemia (FH) variants in UK Biobank.**

The figure shows the quintiles of the predicted probability of any likely pathogenic FH genetic variants estimated from a logistic regression model in UK Biobank participants. The predicted probability is compared with the observed prevalence of any FH variants in the UK Biobank population within each quintile.



**Figure 3. Estimated familial hypercholesterolemia (FH) screening yield in US adults.**

**A**, The figure shows the estimated number of US adults (in millions) from the National Health and Nutrition Examination Survey that could be screened for FH when minimum age threshold for screening increases from  $\geq 20$  to  $\geq 80$  years. **B**, The figure shows the corresponding estimated total number of FH cases that would be identified. **C**, The figure shows the corresponding estimated screening yield (FH cases identified per 1000 individuals screened). The screening strategies considered include the modified Dutch Lipid Clinic Network clinical criteria alone, genetic testing alone, and combining clinical criteria with genetic testing.

combining clinical criteria with genetic testing could yield 6.6 FH cases per 1000 people screened, identifying 1 145 900 FH cases among US adults. Adding genetic testing to clinical criteria screening in targeted groups may improve FH screening yield (eg, adults with an LDL  $\geq 160$  mg/dL and young adults aged

20–39 years) and could allow initiation of early preventive therapy.

Prior studies have estimated the prevalence of FH in the United States without considering genetic testing.<sup>1,3,21</sup> There is limited evidence on the impact of combining clinical criteria with genetic testing on screening yield.<sup>22</sup> There has been little or no examination of FH screening strategies that include genetic testing in young adults, the population most likely to benefit from early preventive treatment when FH is diagnosed.<sup>15</sup> One study in the Geisinger Health System found that 23.7% of patients with an FH variant also had a DLCN clinical criteria score  $\geq 6$  (ie, DLCN criteria ignoring presence of FH variants).<sup>23</sup> Our analysis estimated a similar proportion of FH cases identified by genetic testing, 25.1%, would have a DLCN clinical criteria score  $\geq 6$ . Our approach also assumed that FH cases would be equivalent regardless of if they were based on clinical criteria or FH variant status. Relative to screening using clinical criteria alone, our model estimated that genetic testing alone could identify a greater proportion of FH cases in young adults aged 20 to 39 years than those aged  $\geq 40$  years. This is likely because young adults with FH have not developed some of the clinical criteria that may result in an FH diagnosis (eg, personal history of early ASCVD) that would more likely occur in middle and older ages after a lifetime of high LDL-C exposure. Other studies suggest that FH screening with genetic testing may be more efficient and feasible in children, leading to greater population health benefits attributable to early dietary or even pharmacologic interventions.<sup>10</sup> A clinical trial in the United Kingdom reported on the feasibility and screening yield (in the children screened and their adult parents) of infant FH screening using heel-stick blood samples.<sup>24</sup>

Despite the 2018 American College of Cardiology/AHA cholesterol guidelines recommending that all US adults aged  $\geq 20$  years not already on lipid-lowering therapy undergo lipid measurements to estimate ASCVD risk and establish baseline values, there is limited evidence on the diagnostic yield of screening and relative lack of awareness and lipid testing among younger adults.<sup>12,25</sup> Around two thirds of US adults report having their cholesterol checked, but those aged  $\geq 40$  years are 2.5 to 2.7 times more likely to be aware of a hypercholesterolemia diagnosis than those aged  $< 40$  years.<sup>21,26</sup> As FH screening goes beyond measuring lipids alone, collecting accurate personal and family history information, patient symptoms, and genetics, it is likely that the number of young adults with FH screening is even lower. Our results identified potential subgroups of US adults, for whom FH screening may be especially beneficial. In some groups that we examined, an FH diagnosis may not alter treatment decisions (eg, those with an LDL-C  $\geq 190$  mg/dL for whom high-intensity statins are

**Table 4. Estimated Screening Yield of the DLCN Criteria and Genetic Testing to Identify FH Among US Adults**

Group	No. screened	FH cases (FH cases per 1000 screened)		
		Clinical criteria alone	Genetic testing alone	Combined clinical criteria with genetic testing
Overall	174 523 100	652 100 (3.7)	659 000 (3.8)	1 145 900 (6.6)
Age group, y				
20–39	67 029 600	89 000 (1.3)*	233 300 (3.5)	283 300 (4.2)
40–59	67 179 400	365 800 (5.4)	298 900 (4.4)	574 400 (8.6)
≥60	40 314 200	197 300 (4.9)	126 800 (3.1)	288 200 (7.1)
Observed LDL-C, mg/dL				
<130	111 319 000	0 (0.0)	122 200 (1.1)*	122 200 (1.1)*
130–159	41 457 800	80 100 (1.9)*	127 300 (3.1)*	203 500 (4.9)
160–189	16 283 200	149 700 (9.2)	117 600 (7.2)*	254 600 (15.6)
≥190	5 463 148	422 500 (77.3)	292 000 (53.4)	565 800 (103.6)
Untreated LDL-C, mg/dL				
<130	100 890 900	0 (0.0)	67 600 (0.7)*	67 600 (0.7)*
130–159	43 798 500	0 (0.0)	88 800 (2.0)*	88 800 (2.0)*
160–189	19 836 100	0 (0.0)	98 200 (5.0)*	98 200 (5.0)*
≥190	9 997 600	652 100 (65.2)	404 300 (40.4)	891 200 (89.1)
Aged ≥40 y with 10-y ASCVD risk, %				
<7.5	61 495 400	156 900 (2.6)	200 100 (3.3)	328 000 (5.3)
≥7.5	45 998 100	406 200 (8.8)	225 600 (4.9)	534 600 (11.6)
Hypertension	61 968 400	427 800 (6.9)	300 800 (4.9)	637 700 (10.3)
Not on lipid-lowering treatment	151 198 600	192 500 (1.1)	384 900 (2.2)	507 300 (2.9)

The table shows the estimated screening yield of identifying FH cases in US adults in the National Health and Nutrition Examination Survey using the modified DLCN criteria alone, genetic testing alone, and combining clinical criteria with genetic testing. The number screened is the estimated number of US adults within each group who may be screened. Cases are the number of people with FH identified by screening and the cases per 1000 screened is how many people would be identified if 1000 were screened for FH. CIs are shown in Table S3. ASCVD indicates atherosclerotic cardiovascular disease; DLCN, Dutch Lipid Clinic Network; FH, familial hypercholesterolemia; and LDL-C, low-density lipoprotein cholesterol.

\*The relative SE (ie,  $[SE/case\ prevalence] \times 100\%$ ) was  $>30\%$  and/or the relative CI width (ie,  $[CI\ width/case\ prevalence] \times 100\%$ ) was  $\geq 130\%$ . According to National Health and Nutrition Examination Survey and National Center for Health Statistics reporting criteria, these estimates should be interpreted with caution.

currently recommended).<sup>12</sup> However, in subgroups for whom decisions about lipid-lowering treatment may be less certain (eg, young adults, those with an LDL-C between 160 and 189 mg/dL, or those with a 10-year ASCVD risk score  $<7.5\%$ ), we quantified the potential FH screening yield that can be used to inform FH screening policy and clinical treatment decisions. Data from the Familial Hypercholesterolemia Studies Collaboration show that median age of FH diagnosis is 46 years.<sup>27</sup> National FH screening programs could lead to earlier identification and treatment of individuals with FH to reduce the risk of premature ASCVD.<sup>15</sup> In addition, a national genetic screening program for FH young adults in Australia was found to be cost-effective.<sup>28</sup>

## Limitations

National population-level data on FH variants in the United States do not exist, so we used a prediction model to estimate prevalence. Our prediction model was based on adults from the United Kingdom aged

40 to 69 years and may not be generalizable to the more racially diverse US population and to younger adults. However, our predictive model-based analysis did not show substantial variation in the probability of an FH variant across different age groups; therefore, this may have a limited impact on our results. Future research should examine FH variants in more racially diverse and younger populations. While keeping in mind that race is a social construct, there remains a critical need for more racial diversity in gene identification research. In addition, our model has not been externally validated, and future research should determine if the relationships we observed in the UK Biobank are maintained in other data sources. Our analysis may underestimate the prevalence of FH based on clinical criteria alone because we used modified criteria to match the availability of data in NHANES.<sup>3</sup> Arcus cornealis before the age of 45 years and tendinous xanthomata can be identified on physical examination and are indicative of FH, but the proportion of individuals with FH presenting with them is unclear.<sup>29–31</sup> In addition, family



history of high LDL-C was not available. Because of the low prevalence of FH, we were unable to ensure stable estimates when examining more specific subgroups (eg, combining age and LDL-C strata). Future research is needed to examine the potential benefits of FH screening in more targeted populations. Finally, our analysis did not address the long-term costs and health consequences from FH screening and resulting treatment. These need to be addressed in future research.

## CONCLUSIONS

In this study, we used individual clinical criteria and genotype data from the UK Biobank to predict the probability of any FH variants and then used clinical data from NHANES to estimate FH screening yields in US adults. Clinical criteria-based screening would identify 3.7 FH cases per 1000 US adults screened; and adding genetic testing would increase this to 6.6 FH cases per 1000 screened. Targeted screening strategies, such as offering genetic testing to adults with an LDL-C  $\geq 160$  mg/dL or adults aged 20 to 39 years, may increase screening yield, and could allow for earlier identification and treatment of FH.

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### Supplemental Material

Tables S1–S6

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## **SUPPLEMENTAL MATERIAL**

**Table S1. Characteristics of UK Biobank Participants by FH Variant Status.**

<b>Characteristics</b>	<b>Any FH Variants</b>	<b>No FH Variants</b>	<b>p-value</b>
<i>N</i>	131	49,607	
<i>Demographic</i>			
Age, (years)	56.9 (8.1)	57.1 (8.0)	0.86
Female	65.6%	54.5%	0.01
Race			0.85
White	93.1%	93.4%	
Black	1.5%	2.0%	
Other	5.3%	4.6%	
<i>Cholesterol</i>			
LDL-C, (mg/dL)	159.9 (49.6)	136.5 (33.2)	<0.001
HDL-C, (mg/dL)	56.0 (13.9)	56.9 (14.9)	0.48
Triglycerides, (mg/dL)*	113.9 [82.6, 169.7]	128.1 [90.9, 183.6]	0.02
Total cholesterol, (mg/dL)	243.7 (66.6)	219.5 (43.8)	<0.001
Use of any lipid-lowering therapy	60.0%	19.5%	<0.001
<i>Other Clinical</i>			
BMI	27.8 (5.4)	27.4 (4.8)	0.34
Hypertension	35.2%	29.4%	0.18
SBP	139.0 (19.0)	139.0 (19.0)	0.85
DBP	80.0 (10.0)	82.0 (11.0)	0.10
Diabetes	6.1%	5.9%	1.00
Personal history of ASCVD	13.7%	4.8%	<0.001
Family history of CHD	66.4%	46.0%	<0.001
Family history of stroke	29.0%	28.4%	0.95
Smoking status			0.97
Never	57.0%	56.0%	
Former	34.0%	35.0%	
Current	9.0%	9.0%	

ASCVD – atherosclerotic cardiovascular disease, BMI – body mass index, CHD – coronary heart disease, DBP – diastolic blood pressure, HDL-C – high-density lipoprotein cholesterol, LDL-C – low-density lipoprotein cholesterol, SBP – systolic blood pressure.

Notes: The table shows the participant characteristics at the time of enrollment in UK Biobank by FH variant status. Values are presented as mean (standard deviation) and percentages.

\*Triglycerides are reported as median [interquartile range]



**Table S2. Characteristics of NHANES Participants with Complete Data.**

<b>Characteristics</b>	<b>Complete Case Analysis</b>
<i>N</i>	16,103
<i>Demographic</i>	
Age, (years)	45.9 (16.3)
Female	48.7%
Race	
White	68.5%
Black	11.3%
Hispanic	13.8%
Other	6.4%
<i>Cholesterol</i>	
LDL-C, (mg/dL)*	118.9 (35.2)
HDL-C, (mg/dL)	53.7 (15.9)
Triglycerides, (mg/dL)†	104.0 [73.0 - 152.0]
Total cholesterol, (mg/dL)	194.6 (39.6)
Use of any lipid-lowering therapy	13.4%
<i>Other Clinical</i>	
BMI	28.4 (6.5)
Hypertension	34.4%
SBP	121.3 (16.9)
DBP	70.8 (10.8)
Diabetes	7.6%
Personal history of ASCVD	6.8%
Family history of early CHD	12.1%
Family history of stroke	-
Smoking status	
Never	53.7%
Former	24.4%
Current	21.9%

ASCVD – atherosclerotic cardiovascular disease, BMI – body mass index, CHD – coronary heart disease, DBP – diastolic blood pressure, HDL-C – high-density lipoprotein cholesterol, LDL-C – low-density lipoprotein cholesterol, NHANES – National Health and Nutrition Examination Survey, SBP – systolic blood pressure.

Notes: The table shows NHANES participant characteristics at the time of the examination for those with no missing data on characteristics. Values are presented as mean (standard deviation) and percentages.

\*LDL-C was calculated using the Sampson formula

†Triglycerides are reported as median [interquartile range]

**Table S3. Probability of Any FH Variants in US Adults.**

<b>Group</b>	<b>Probability of Any FH Variants, % (95%CI)</b>	
	<b>Primary Analysis (Multiply Imputed Data)</b>	<b>Complete Case Analysis</b>
<i>Overall</i>	0.38% (0.33% - 0.42%)	0.37% (0.32% - 0.43%)
<i>Age Category</i>		
20-39 years	0.35% (0.29% - 0.42%)	0.36% (0.27% - 0.47%)
40-59 years	0.44% (0.37% - 0.53%)	0.41% (0.33% - 0.51%)
≥60 years	0.31% (0.26% - 0.37%)	0.31% (0.24% - 0.39%)
<i>Race</i>		
White	0.37% (0.32% - 0.43%)	0.37% (0.31% - 0.44%)
Black	0.45% (0.38% - 0.53%)	0.51% (0.38% - 0.65%)
Hispanic	0.35% (0.24% - 0.50%)	0.24% (0.21% - 0.27%)
Other	0.39% (0.24% - 0.60%)	0.45% (0.15% - 1.03%)
<i>Observed LDL-C (mg/dL)</i>		
<130	0.11% (0.11% - 0.12%)	0.12% (0.11% - 0.12%)
130-159	0.31% (0.28% - 0.33%)	0.29% (0.27% - 0.32%)
160-189	0.72% (0.63% - 0.81%)	0.69% (0.62% - 0.77%)
≥190	5.32% (4.10% - 6.77%)	5.58% (4.06% - 7.46%)
<i>Untreated LDL-C (mg/dL)</i>		
<130	0.07% (0.07% - 0.07%)	0.07% (0.07% - 0.07%)
130-159	0.20% (0.20% - 0.21%)	0.22% (0.20% - 0.23%)
160-189	0.49% (0.46% - 0.52%)	0.51% (0.48% - 0.54%)
≥190	4.04% (3.33% - 4.84%)	4.24% (3.35% - 5.29%)
<i>Aged ≥40 Years with 10-year ASCVD Risk</i>		
<7.5%	0.32% (0.28% - 0.38%)	0.37% (0.29% - 0.46%)
≥7.5%	0.49% (0.38% - 0.63%)	0.39% (0.32% - 0.47%)
<i>Hypertension</i>	0.48% (0.41% - 0.57%)	0.44% (0.37% - 0.53%)
<i>Not Using Lipid-Lowering Treatment</i>	0.22% (0.19% - 0.25%)	0.22% (0.18% - 0.27%)

ASCVD – atherosclerotic cardiovascular disease, FH – familial hypercholesterolemia, LDL-C – low-density lipoprotein cholesterol, 95%CI – 95% confidence interval.

Notes: The table shows the probability of any FH-causative genetic variants when applying the logistic regression model from the UK Biobank to National Health and Nutrition Examination Survey (NHANES) participants. Results are shown for the primary analysis, in which missing data were multiply imputed in NHANES participants, and in the complete cases analysis, in which only participants with complete data on needed variables were included.

**Table S4. Estimated FH Screening Yield Among US Adults.**

Group	Primary Analysis (Multiply Imputed Data)		Complete Case Analysis	
	Cases (95%CI)	Cases per 1000 Screened (95%CI)	Cases (95%CI)	Cases per 1000 Screened (95%CI)
<b>Overall</b>				
Number screened	174,523,100 (172,682,700 - 176,336,200)		174,523,100 (172,682,700 - 176,336,200)	
Clinical criteria alone	652,100 (523,200 - 803,000)	3.7 (3.0 - 4.6)	499,500 (335,200 - 716,000)	2.9 (1.9 - 4.1)
Genetic testing alone	659,000 (478,600 - 885,800)	3.8 (2.7 - 5.1)	631,100 (436,200 - 883,800)	3.6 (2.5 - 5.1)
Total combined	1,145,900 (931,100 - 1,395,400)	6.6 (5.3 - 8.0)	1,021,000 (770,400 - 1,327,100)	5.9 (4.4 - 7.6)
<i>Age Category</i>				
20-39 years				
Number screened	67,029,600 (65,305,300 - 68,766,500)		68,525,100 (66,266,200 - 70,804,000)	
Clinical criteria alone	89,000 (40,000 - 170,800)*	1.3 (0.6 - 2.5)*	78,300 (22,200 - 196,000)*	1.1 (0.3 - 2.9)*
Genetic testing alone	233,300 (135,400 - 375,200)	3.5 (2.0 - 5.6)	242,500 (129,200 - 416,000)	3.5 (1.9 - 6.1)
Total combined	283,300 (177,300 - 429,800)	4.2 (2.6 - 6.4)	290,400 (164,300 - 475,900)	4.2 (2.4 - 6.9)
40-59 years				
Number screened	67,179,400 (65,840,000 - 68,526,300)		67,540,800 (65,677,500 - 69,418,400)	
Clinical criteria alone	365,800 (264,200 - 493,400)	5.4 (3.9 - 7.3)	236,400 (123,000 - 410,600)	3.5 (1.8 - 6.1)
Genetic testing alone	298,900 (176,700 - 473,800)	4.4 (2.6 - 7.1)	271,000 (144,800 - 463,300)	4.0 (2.1 - 6.9)



Group	Primary Analysis (Multiply Imputed Data)		Complete Case Analysis	
	Cases (95%CI)	Cases per 1000 Screened (95%CI)	Cases (95%CI)	Cases per 1000 Screened (95%CI)
Total combined	574,400 (423,500 - 761,400)	8.6 (6.3 - 11.3)	464,700 (293,100 - 700,000)	6.9 (4.3 - 10.4)
≥60 years				
Number screened	40,314,200 (38,927,800 - 41,726,000)		38,457,200 (36,720,800 - 40,236,800)	
Clinical criteria alone	197,300 (127,600 - 291,100)	4.9 (3.2 - 7.2)	184,800 (94,000 - 326,300)	4.8 (2.4 - 8.5)
Genetic testing alone	126,800 (65,100 - 222,900)	3.1 (1.6 - 5.5)	117,600 (54,900 - 221,100)*	3.1 (1.4 - 5.7)*
Total combined	288,200 (195,800 - 408,900)	7.1 (4.9 - 10.1)	266,000 (157,300 - 420,900)	6.9 (4.1 - 10.9)
<i>Observed LDL-C</i>				
<130 mg/dL				
Number screened	111,319,000 (110,107,700 - 112,522,800)		113,052,900 (111,317,700 - 114,771,500)	
Clinical criteria alone	0 (0 - 0)	0.0 (0.0 - 0.0)	0 (0 - 0)	0.0 (0.0 - 0.0)
Genetic testing alone	122,200 (51,700 - 245,400)*	1.1 (0.5 - 2.2)*	126,900 (52,100 - 261,600)*	1.1 (0.5 - 2.3)*
Total combined	122,200 (51,700 - 245,400)*	1.1 (0.5 - 2.2)*	126,900 (52,100 - 261,600)*	1.1 (0.5 - 2.3)*
130-159 mg/dL				
Number screened	41,457,800 (40,482,100 - 42,445,500)		40,455,700 (38,961,600 - 41,979,200)	
Clinical criteria alone	80,100 (35,600 - 154,800)*	1.9 (0.9 - 3.7)*	48,100 (6,400 - 168,000)*,†	1.2 (0.2 - 4.2)*,†

Group	Primary Analysis (Multiply Imputed Data)		Complete Case Analysis	
	Cases (95%CI)	Cases per 1000 Screened (95%CI)	Cases (95%CI)	Cases per 1000 Screened (95%CI)
Genetic testing alone	127,300 (57,400 - 244,600)*	3.1 (1.4 - 5.9)*	113,700 (45,700 - 236,900)*	2.8 (1.1 - 5.9)*
Total combined	203,500 (117,000 - 329,200)	4.9 (2.8 - 7.9)	160,100 (71,400 - 310,700)*	4.0 (1.8 - 7.7)*
160-189 mg/dL				
Number screened	16,283,200 (15,516,400 - 17,075,100)		15,864,100 (14,833,100 - 16,942,300)	
Clinical criteria alone	149,700 (83,300 - 247,400)	9.2 (5.1 - 15.2)	139,300 (65,000 - 260,200)*	8.8 (4.1 - 16.4)*
Genetic testing alone	117,600 (52,800 - 226,300)*	7.2 (3.2 - 13.9)*	108,400 (43,900 - 224,500)*	6.8 (2.8 - 14.2)*
Total combined	254,600 (159,200 - 385,900)	15.6 (9.8 - 23.7)	236,500 (133,900 - 386,400)	14.9 (8.4 - 24.4)
≥190 mg/dL				
Number screened	5,463,100 (5,046,200 - 5,904,400)		5,150,500 (4,604,500 - 5,741,800)	
Clinical criteria alone	422,500 (315,400 - 551,800)	77.3 (57.7 - 101.0)	312,100 (185,200 - 488,100)	60.6 (36.0 - 94.8)
Genetic testing alone	292,000 (180,600 - 443,800)	53.4 (33.0 - 81.2)	282,000 (157,700 - 461,500)	54.8 (30.6 - 89.6)
Total combined	565,800 (426,600 - 731,800)	103.6 (78.1 - 133.9)	497,500 (328,500 - 715,000)	96.6 (63.8 - 138.8)
<i>Untreated LDL-C</i>				
<130 mg/dL				
Number screened	100,890,900 (99,576,100 - 102,201,000)		102,245,200 (100,255,200 - 104,223,200)	

Group	Primary Analysis (Multiply Imputed Data)		Complete Case Analysis	
	Cases (95%CI)	Cases per 1000 Screened (95%CI)	Cases (95%CI)	Cases per 1000 Screened (95%CI)
Clinical criteria alone	0 (0 - 0)	0.0 (0.0 - 0.0)	0 (0 - 0)	0.0 (0.0 - 0.0)
Genetic testing alone	67,600 (20,300 - 166,700)*	0.7 (0.2 - 1.7)*	68,600 (20,200 - 174,100)*	0.7 (0.2 - 1.7)*
Total combined	67,600 (20,300 - 166,700)*	0.7 (0.2 - 1.7)*	68,600 (20,200 - 174,100)*	0.7 (0.2 - 1.7)*
130-159 mg/dL				
Number screened	43,798,500 (42,758,100 - 44,851,300)		43,591,400 (42,003,200 - 45,209,100)	
Clinical criteria alone	0 (0 - 0)	0.0 (0.0 - 0.0)	0 (0 - 0)	0.0 (0.0 - 0.0)
Genetic testing alone	88,800 (31,900 - 197,100)*	2.0 (0.7 - 4.5)*	87,800 (29,700 - 205,000)*	2.0 (0.7 - 4.7)*
Total combined	88,800 (31,900 - 197,100)*	2.0 (0.7 - 4.5)*	87,800 (29,700 - 205,000)*	2.0 (0.7 - 4.7)*
160-189 mg/dL				
Number screened	19,836,100 (19,019,600 - 20,675,200)		19,694,900 (18,533,000 - 20,903,500)	
Clinical criteria alone	0 (0 - 0)	0.0 (0.0 - 0.0)	0 (0 - 0)	0.0 (0.0 - 0.0)
Genetic testing alone	98,200 (37,900 - 208,600)*	5.0 (1.9 - 10.5)*	98,200 (35,100 - 220,100)*	5.0 (1.8 - 11.2)*
Total combined	98,200 (37,900 - 208,600)*	5.0 (1.9 - 10.5)*	98,200 (35,100 - 220,100)*	5.0 (1.8 - 11.2)*
≥190 mg/dL				
Number screened	9,997,600 (9,449,700 - 10,567,600)		8,991,600 (8,216,400 - 9,817,100)	

Group	Primary Analysis (Multiply Imputed Data)		Complete Case Analysis	
	Cases (95%CI)	Cases per 1000 Screened (95%CI)	Cases (95%CI)	Cases per 1000 Screened (95%CI)
Clinical criteria alone	652,100 (526,200 - 797,300)	65.2 (52.6 - 79.7)	499,500 (338,600 - 706,600)	55.6 (37.7 - 78.6)
Genetic testing alone	404,300 (269,600 - 580,900)	40.4 (27.0 - 58.1)	376,500 (232,000 - 574,800)	41.9 (25.8 - 63.9)
Total combined	891,200 (718,400 - 1,090,000)	89.1 (71.9 - 109.0)	766,500 (556,200 - 1,024,000)	85.2 (61.9 - 113.9)
<i>Adults Aged ≥40 Years with 10-year ASCVD Risk</i>				
<i>&lt;7.5%</i>				
Number screened	61,495,400 (60,082,900 - 62,919,100)		63,768,500 (61,900,800 - 65,653,700)	
Clinical criteria alone	156,900 (86,500 - 261,600)	2.6 (1.4 - 4.3)	156,600 (60,200 - 331,200)*	2.5 (0.9 - 5.2)*
Genetic testing alone	200,100 (102,300 - 353,200)	3.3 (1.7 - 5.7)	230,100 (113,000 - 417,700)*	3.6 (1.8 - 6.5)*
Total combined	328,000 (207,500 - 493,000)	5.3 (3.4 - 8.0)	346,700 (193,100 - 573,900)	5.4 (3.0 - 9.0)
<i>≥7.5%</i>				
Number screened	45,998,100 (44,580,200 - 47,437,400)		42,229,500 (40,519,300 - 43,975,900)	
Clinical criteria alone	406,200 (305,300 - 529,300)	8.8 (6.6 - 11.5)	264,700 (163,700 - 404,500)	6.3 (3.9 - 9.6)
Genetic testing alone	225,600 (133,200 - 358,000)	4.9 (2.9 - 7.8)	158,500 (82,400 - 276,600)	3.8 (2.0 - 6.6)
Total combined	534,600 (406,200 - 690,400)	11.6 (8.8 - 15.0)	383,900 (256,700 - 551,900)	9.1 (6.1 - 13.1)

Group	Primary Analysis (Multiply Imputed Data)		Complete Case Analysis	
	Cases (95%CI)	Cases per 1000 Screened (95%CI)	Cases (95%CI)	Cases per 1000 Screened (95%CI)
<i>Hypertension</i>				
Number screened	61,968,400 (60,445,300 - 63,504,200)		60,089,100 (57,947,200 - 62,258,500)	
Clinical criteria alone	427,800 (335,300 - 537,800)	6.9 (5.4 - 8.7)	340,700 (218,800 - 505,900)	5.7 (3.6 - 8.4)
Genetic testing alone	300,800 (190,600 - 451,900)	4.9 (3.1 - 7.3)	252,600 (142,200 - 415,200)	4.2 (2.4 - 6.9)
Total combined	637,700 (499,500 - 802,200)	10.3 (8.1 - 12.9)	544,400 (377,300 - 759,800)	9.1 (6.3 - 12.6)
<i>Not on Lipid-Lowering Treatment</i>				
Number screened	151,198,600 (149,713,500 - 152,626,100)		151,198,600 (149,713,500 - 152,626,100)	
Clinical criteria alone	192,500 (113,500 - 305,500)	1.1 (0.7 - 1.8)	141,200 (55,000 - 296,400)*	0.9 (0.4 - 2.0)*
Genetic testing alone	384,900 (241,300 - 583,300)	2.2 (1.4 - 3.3)	321,500 (187,700 - 515,700)	2.1 (1.2 - 3.4)
Total combined	507,300 (346,900 - 716,900)	2.9 (2.0 - 4.1)	423,500 (263,100 - 646,400)	2.8 (1.7 - 4.3)

ASCVD – atherosclerotic cardiovascular disease, BMI – body mass index, FH – familial hypercholesterolemia, LDL-C – low-density lipoprotein cholesterol, 95%CI – 95% confidence interval.



Notes: The table shows the estimated screening yield of using the Dutch Lipid Clinic Network criteria with and without genetic testing in US adults from NHANES. The number screened is the estimated number of US adults meeting the specified criteria. Cases are the number of persons with FH identified by screening and the cases per 1000 screened is how many persons would be identified if 1000 were screened for FH. Results are shown for the primary analysis, in which missing data were multiply imputed in NHANES participants, and in the complete cases analysis, in which only participants with complete data on needed variables were included.

\*The relative standard error (i.e.,  $[\text{standard error}/\text{case prevalence}] * 100\%$ ) was  $>30\%$  and/or the relative confidence interval width (i.e.,  $[\text{confidence interval width}/\text{case prevalence}] * 100\%$ ) was  $\geq 130\%$ . According to National Health and Nutrition Examination Survey (NHANES) and National Center for Health Statistics (NCHS) reporting criteria, these estimates should be interpreted with caution.

†Unweighted number of FH cases identified was  $<5$ . According to NHANES and NCHS reporting criteria, these estimates should be interpreted with caution.

**Table S5. Estimated FH Screening Yield Using American Heart Association Clinical Criteria Among US Adults.**

Group	Primary Analysis (Multiply Imputed Data)		Complete Case Analysis	
	Cases (95%CI)	Cases per 1000 Screened (95%CI)	Cases (95%CI)	Cases per 1000 Screened (95%CI)
<b>Overall</b>				
Clinical criteria alone	2,047,600 (1,794,400 - 2,326,200)	11.7 (10.3 - 13.3)	1,718,800 (1,383,700 - 2,109,900)	9.8 (7.9 - 12.1)
Total combined	2,290,900 (1,889,400 - 2,778,300)	13.1 (10.8 - 15.9)	2,018,500 (1,519,300 - 2,646,000)	11.6 (8.7 - 15.2)
<i>Age Category</i>				
20-39 years				
Clinical criteria alone	249,900 (170,400 - 353,600)	3.7 (2.5 - 5.3)	152,400 (67,100 - 296,200)*	2.2 (1.0 - 4.3)*
Total combined	377,000 (209,400 - 629,600)	5.6 (3.1 - 9.4)	335,800 (134,300 - 683,900)	4.9 (2.0 - 10.0)
40-59 years				
Clinical criteria alone	1,070,400 (856,100 - 1,321,400)	15.9 (12.7 - 19.7)	950,200 (690,600 - 1,274,200)	14.1 (10.2 - 18.9)
Total combined	1,152,000 (852,900 - 1,555,500)	17.1 (12.7 - 23.2)	1,062,000 (709,900 - 1,554,700)	15.7 (10.5 - 23.0)
≥60 years				
Clinical criteria alone	727,300 (602,700 - 869,700)	18.0 (14.9 - 21.6)	616,300 (446,700 - 828,200)	16.0 (11.6 - 21.5)
Total combined	761,900 (595,800 - 986,600)	18.9 (14.8 - 24.5)	620,700 (427,700 - 891,700)	16.1 (11.1 - 23.2)

Group	Primary Analysis (Multiply Imputed Data)		Complete Case Analysis	
	Cases (95%CI)	Cases per 1000 Screened (95%CI)	Cases (95%CI)	Cases per 1000 Screened (95%CI)
<i>Observed LDL-C</i>				
<i>&lt;130 mg/dL</i>				
Clinical criteria alone	0 (0 - 0)	0.0 (0.0 - 0.0)	0 (0 - 0)	0.0 (0.0 - 0.0)
Total combined	122,200 (51,700 - 245,400)*	1.1 (0.5 - 2.2)*	126,900 (52,100 - 261,600)*	1.1 (0.5 - 2.3)*
<i>130-159 mg/dL</i>				
Clinical criteria alone	767,400 (613,900 - 947,000)	18.5 (14.8 - 22.8)	643,200 (459,900 - 874,200)	15.9 (11.4 - 21.6)
Total combined	823,900 (617,200 - 1,102,500)	19.9 (14.9 - 26.6)	707,300 (470,100 - 1,053,700)	17.5 (11.6 - 26.0)
<i>160-189 mg/dL</i>				
Clinical criteria alone	359,300 (262,100 - 480,100)	22.1 (16.1 - 29.5)	317,600 (200,300 - 477,300)	20.0 (12.6 - 30.1)
Total combined	402,700 (257,200 - 632,200)	24.7 (15.8 - 38.8)	367,700 (203,100 - 634,900)	23.2 (12.8 - 40.0)
<i>≥190 mg/dL</i>				
Clinical criteria alone	921,100 (754,300 - 1,108,000)	168.6 (138.1 - 202.8)	758,000 (549,800 - 1,008,100)	147.2 (106.7 - 195.7)
Total combined	942,200 (739,200 - 1,172,600)	172.5 (135.3 - 214.6)	816,600 (558,000 - 1,133,000)	158.5 (108.3 - 220.0)
<i>Untreated LDL-C</i>				
<i>&lt;130 mg/dL</i>				

Group	Primary Analysis (Multiply Imputed Data)		Complete Case Analysis	
	Cases (95%CI)	Cases per 1000 Screened (95%CI)	Cases (95%CI)	Cases per 1000 Screened (95%CI)
Clinical criteria alone	0 (0 - 0)	0.0 (0.0 - 0.0)	0 (0 - 0)	0.0 (0.0 - 0.0)
Total combined	67,600 (20,300 - 166,700)*	0.7 (0.2 - 1.7)*	68,600 (20,200 - 174,100)*	0.7 (0.2 - 1.7)*
130-159 mg/dL				
Clinical criteria alone	0 (0 - 0)	0.0 (0.0 - 0.0)	0 (0 - 0)	0.0 (0.0 - 0.0)
Total combined	88,800 (31,900 - 197,100)*	2.0 (0.7 - 4.5)*	87,800 (29,700 - 205,000)*	2.0 (0.7 - 4.7)*
160-189 mg/dL				
Clinical criteria alone	0 (0 - 0)	0.0 (0.0 - 0.0)	0 (0 - 0)	0.0 (0.0 - 0.0)
Total combined	98,200 (37,900 - 208,600)*	5.0 (1.9 - 10.5)*	98,200 (35,100 - 220,100)*	5.0 (1.8 - 11.2)
≥190 mg/dL				
Clinical criteria alone	1,909,200 (1,661,200 - 2,177,000)	191.0 (166.2 - 217.8)	1,608,400 (1,314,600 - 1,936,800)	178.9 (146.2 - 215.4)
Total combined	2,036,300 (1,748,400 - 2,350,800)	203.7 (174.9 - 235.1)	1,763,900 (1,413,100 - 2,161,000)	196.2 (157.2 - 240.3)
<i>Adults Aged ≥40 Years with 10-year ASCVD Risk &lt;7.5%</i>				
Clinical criteria alone	713,700 (541,900 - 922,100)	11.6 (8.8 - 15.0)	779,000 (538,400 - 1,089,200)	12.2 (8.4 - 17.1)
Total combined	786,700 (540,200 - 1,137,900)	12.8 (8.8 - 18.5)	860,800 (542,700 - 1,322,500)	13.5 (8.5 - 20.7)

Group	Primary Analysis (Multiplied Imputed Data)		Complete Case Analysis	
	Cases (95%CI)	Cases per 1000 Screened (95%CI)	Cases (95%CI)	Cases per 1000 Screened (95%CI)
$\geq 7.5\%$				
Clinical criteria alone	1,084,000 (924,400 - 1,262,800)	23.6 (20.1 - 27.5)	787,500 (599,400 - 1,015,000)	18.6 (14.2 - 24.0)
Total combined	1,127,000 (912,000 - 1,412,000)	24.5 (19.8 - 30.7)	821,800 (588,600 - 1,146,500)	19.5 (13.9 - 27.1)
<i>Hypertension</i>				
Clinical criteria alone	1,184,700 (995,400 - 1,399,100)	19.1 (16.1 - 22.6)	1,027,800 (792,000 - 1,310,700)	17.1 (13.2 - 21.8)
Total combined	1,313,600 (1,050,300 - 1,658,500)	21.2 (16.9 - 26.8)	1,158,400 (840,200 - 1,599,400)	19.3 (14.0 - 26.6)
<i>Not on Lipid-Lowering Treatment</i>				
Clinical criteria alone	801,800 (620,800 - 1,018,900)	4.6 (3.6 - 5.8)	582,900 (392,300 - 833,500)	3.9 (2.6 - 5.5)
Total combined	1,124,000 (791,300 - 1,543,100)	6.4 (4.5 - 8.8)	855,800 (519,400 - 1,329,400)	5.7 (3.4 - 8.8)

AHA – American Heart Association, ASCVD – atherosclerotic cardiovascular disease, FH – familial hypercholesterolemia, LDL-C – low-density lipoprotein cholesterol, 95%CI – 95% confidence interval.

Notes: The table shows the Estimated screening yield of using the AHA criteria with and without genetic testing in US adults from NHANES. The number screened and FH cases identified by genetic testing are shown in **Table S3**. Cases are the number of persons with FH identified by screening and the cases per 1000 screened is how many persons would be identified if 1000 were screened for FH. Results are shown for the primary analysis, in which missing data were multiply imputed in NHANES participants, and in the complete cases analysis, in which only participants with complete data on needed variables were included.

\*The relative standard error (i.e., [standard error/case prevalence]\*100%) was >30% and/or the relative confidence interval width (i.e., [confidence interval width/case prevalence]\*100%) was  $\geq$ 130%. According to National Health and Nutrition Examination Survey (NHANES) and National Center for Health Statistics (NCHS) reporting criteria, these estimates should be interpreted with caution.

**Table S6. LDL-C and FH Cases Identified with Different LDL-C Equations.**

<b>Characteristic</b>	<b>Friedewald</b>	<b>Martin-Hopkins</b>	<b>Sampson</b>
<i>Primary Analysis (Multiply Imputed Data)</i>			
LDL-C (mg/dL)	117.3 (35.5)	119.5 (35.9)	119.7 (35.8)
Screening yield (per 1000 screened)	3.2 (2.4 - 4.1)	3.9 (3.2 - 4.7)	3.7 (3.0 - 4.6)
<i>Complete Case Analysis</i>			
LDL-C (mg/dL)	116.6 (35.0)	118.1 (34.8)	118.9 (35.2)
Screening yield (per 1000 screened)	2.6 (1.8 - 3.7)	2.8 (1.8 - 4.0)	2.9 (1.9 - 4.1)

FH – familial hypercholesterolemia, LDL-C – low-density lipoprotein cholesterol.

Notes: The table shows the impact of using different methods to calculate LDL-C in NHANES participants. For the Martin-Hopkins and Sampson formulas, participants with triglycerides <800 mg/dL were included. As the Friedewald equation is used for individuals with triglycerides ≤400 mg/dL, we excluded those with triglycerides >400 mg/dL when estimating the mean LDL-C and screening yield. The screening yield is number of FH cases identified per 1000 screened using the Dutch Lipid Clinic Network Criteria based on clinical criteria only (i.e., without genetic testing). Results are presented as the mean (standard deviation) for LDL-C and mean (95% confidence interval) for screening yield. Results are shown for the primary analysis, in which missing data were multiply imputed in NHANES participants, and in the complete cases analysis, in which only participants with complete data on needed variables were included.