

SUPPLEMENTAL MATERIAL

Table S1. Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolemia*.

Supplementary Table S1 : Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolemia*		
Criteria		Points
Family history	First-degree relative with known premature (men: <55 years; women: <60 years) coronary and vascular disease, or First-degree relative with known LDLC† above the 95th percentile	1
	First-degree relative with tendinous xanthomata and/or arcus cornealis, or Children aged less than 18 years with LDLC above the 95th percentile	2
Clinical history	Patient with premature (men: <55 years; women: <60 years) coronary artery disease	2
	Patient with premature (men: <55 years; women: <60 years) cerebral or peripheral vascular disease	1
Physical examination	Tendinous xanthomata	6
	Arcus cornealis prior to age 45 years	4
Cholesterol levels (mmol/liter)	LDLC, ≥8.5	8
	LDLC, 6.5–8.4	5
	LDLC, 5.0–6.4	3
	LDLC, 4.0–4.9	1
DNA analysis	Functional mutation in the <i>LDLR</i> gene	8
Diagnosis (diagnosis is based on the total number of points obtained)		
A “definite” FH† diagnosis requires more than 8 points		
A “probable” FH diagnosis requires 6–8 points		
A “possible” FH diagnosis requires 3–5 points		
* World Health Organization. Familial hypercholesterolemia—report of a second WHO Consultation. Geneva, Switzerland: World Health Organization, 1999. (WHO publication no. WHO/HGN/FH/CONS/99.2). (15).		
† LDLC, low density lipoprotein cholesterol; FH, familial hypercholesterolemia.		

Table S2. EHR based algorithm based on Dutch Lipid Clinic Network criteria to identify familial hypercholesterolemia.

Dutch Lipid Clinic Network Criteria	Implementation
First-degree relative with premature coronary and/or vascular disease (men \leq 55 years, women \leq 60 years)	<ul style="list-style-type: none"> - Searched for ‘Heart Disease’ in family history (not limited to first-degree relatives as this information was not always available) - Searched for ‘Family history of premature heart disease’ in problem list
First-degree relative with known LDL-C \geq 95th percentile for age and sex	- Searched for ‘Family history of hyperlipidemia in problem list
First-degree relative with tendon xanthomata and/or arcus cornealis,	- Data unavailable
Children aged \leq 18 years with known LDL-C \geq 95th percentile for age and sex	Used known mother/child links (available since 2010) to search for children with LDL \geq 95th percentile (LOINC: 13457-7, 18262-6, 2089-1, 55440-2 and lab result value between 230 and 90000.
Clinical History	
Patient with premature coronary artery disease (men \leq 55 years, women \leq 60 years)	Used electronic phenotyping to identify patients with premature coronary artery disease. Used P004 to pull these patients. A previously validated algorithm.
Patient with premature cerebral or peripheral vascular disease (men \leq 55 years, women \leq 60 years)	<p>Searched for ICD9 diagnosis codes in encounters and problem list (PVD: 249.7, 249.70, 249.71, 250.70, 250.71, 250.73, 440.20, 440.21, 440.22, 440.23, 440.24, 443, 443.0, 443.1, 443.2, 443.21, 443.22, 443.23, 443.24, 443.29, 443.8, 443.81, 443.82, 443.89, 443.9, V12.59</p> <p>CVD: 199.1, 436, 437, 437.0, 437.1, 437.8, 437.9, 438, 438.0, 438.1, 438.10, 438.11, 438.12, 438.13, 438.14, 438.19, 438.2, 438.20, 438.21, 438.22, 438.3, 438.30, 438.31, 438.32, 438.4, 438.40, 438.41, 438.42, 438.5, 438.50, 438.51, 438.52, 438.53, 438.6, 438.7, 438.8, 438.81, 438.82, 438.83, 438.84, 438.85, 438.89, 438.9, 674.0, 674.00, 674.02, V12.59) Patients had to have two or more diagnoses in their EHR.</p>
Physical Examination	
Tendon xanthomata	

	Searched for ICD9 diagnosis codes in encounters and problem list (272.7). Patients had to have two or more diagnoses in their EHR.
Arcus cornealis at age \leq 45 years	Searched for ICD9 diagnosis codes in encounters and problem list (371.41)
LDL-C (mg/dl)	
	- Used maximum lifetime outpatient LDL-C level
LDL-C < 155	
$155 \geq$ LDL-C < 189	
$190 \geq$ LDL-C < 249	
$250 \geq$ LDL-C < 329	
LDL-C \geq 330	
DNA Analysis – functional variant in <i>LDLR</i> , <i>APOB</i> or <i>PCSK9</i> gene	
	<i>LDLR</i>
	<i>APOB</i>
	<i>PCSK9</i>

Table S3. Count of Patients Meeting Each Definition.

Dutch Lipid Clinic Network Criteria	Points	Meeting criteria in EHR, N (%)	Not meeting criteria in EHR, N (%)	Implemented using Modified criteria (below)
First-degree relative with premature coronary and/or vascular disease (men \leq 55 years, women \leq 60 years)	1	108,742 (45.70%)	129,161 (54.29%)	Searched for 'Heart Disease' in family history (not limited to first-degree relatives as this information was not always available) Searched for 'Family history of premature heart disease' in problem list
First-degree relative with known LDL-C \geq 95th percentile for age and sex	1	15 (0.00%)*	237,888 (99.99%)	Searched for 'Family history of hyperlipidemia in problem list
First-degree relative with tendon xanthomata and/or arcus cornealis	2	N/A	N/A	Data unavailable
Children aged \leq 18 years with known LDL-C \geq 95th percentile for age and sex	2	0 (0.00%)*	237,903 (100.00%)	Used known mother/child links (available since 2010) to search for children with LDL \geq 95th percentile (LOINC: 13457-7, 18262-6, 2089-1, 55440-2 where lab value between 230 AND 90000)

Clinical History				
Patient with premature coronary artery disease (men ≤ 55 years, women ≤ 60 years)	2	9,809 (4.12%)	228,094 (95.87%)	Used electronic phenotyping to identify patients with premature coronary artery disease. Used P004 to pull these patients
Patient with premature cerebral or peripheral vascular disease (men ≤ 55 years, women ≤ 60 years)	1	2,722 (1.14%)	235,181 (98.85%)	Searched for ICD9 diagnosis codes in encounters and problem list (PVD: 249.7, 249.70, 249.71, 250.70, 250.71, 250.73, 440.20, 440.21, 440.22, 440.23, 440.24, 443, 443.0, 443.1, 443.2, 443.21, 443.22, 443.23, 443.24, 443.29, 443.8, 443.81, 443.82, 443.89, 443.9, V12.59 CVD: 199.1, 436, 437, 437.0, 437.1, 437.8, 437.9, 438, 438.0, 438.1, 438.10, 438.11, 438.12, 438.13, 438.14, 438.19, 438.2, 438.20, 438.21, 438.22, 438.3, 438.30, 438.31, 438.32, 438.4, 438.40, 438.41, 438.42, 438.5, 438.50, 438.51, 438.52, 438.53, 438.6, 438.7, 438.8, 438.81, 438.82, 438.83, 438.84, 438.85, 438.89, 438.9, 674.0, 674.00, 674.02, V12.59) Patients had to have two or more diagnoses in their EHR.

Physical Examination				
Tendon xanthomata	6	27 (0.00%)*	237,876 (99.99%)	Searched for ICD9 diagnosis codes in encounters and problem list (272.7). Patients had to have two or more diagnoses in their EHR.
Arcus cornealis at age \leq 45 years	4	1 (0.00%)*	237,902 (99.99%)	Searched for ICD9 diagnosis codes in encounters and problem list (371.41). Patients had to have two or more diagnoses in their EHR.
LDL-C (mg/dl)				
None recorded	-	9,573 (4.02%)	-	Used maximum lifetime outpatient LDL-C level (LOINC 13457-7, 18262-6, 2089-1, 55440-2)
LDL-C < 155	0	138,351 (58.12%)	-	
155 \geq LDL-C < 189	1	61,955(26.04%)	-	
190 \geq LDL-C < 249	3	25,494 (10.72%)	-	
250 \geq LDL-C < 329	5	2,178 (0.92%)	-	

LDL-C \geq 330	8	352 (0.15%)	-	
DNA Analysis – functional variant in <i>LDLR</i> , <i>APOB</i> or <i>PCSK9</i> gene (variant data was not available for the entire cohort so %s are not presented).				
<i>LDLR</i>	8	85	-	
<i>APOB</i>	8	76	-	
<i>PCSK9</i>	8	19	-	

Table S4. PPV, NPV, Sensitivity and Specificity to Definitions.

Definition 1	Family history of heart disease		Sensitivity	92.37%
	Def1+	Def1-	Specificity	98.32%
Def1+	121	2	PPV	98.37%
Def1-	10	117	NPV	92.13%
	131	119	Accuracy	95.20%
	250			
Definition 2*	First-degree relative with known LDL-C \geq 95th percentile for age and sex		Sensitivity	0.00%
	Def2+	Def2-	Specificity	100.00%
Def2+	0	0	PPV	N/A
Def2-	2	248	NPV	99.20%
	2	248	Accuracy	99.20%
	250			
Definition 5	Patient with premature coronary artery disease (men \leq 55 years, women \leq 60 years)		Sensitivity	93.94%
	Def5+	Def5-	Specificity	99.54%
Def5+	31	1	PPV	96.88%
Def5-	2	216	NPV	99.08%
	33	217	Accuracy	98.80%
	250			
Definition 6	Patient with premature cerebral or peripheral vascular disease (men \leq 55 years, women \leq 60 years)		Sensitivity	92.86%
	Def6+	Def6-	Specificity	100.00%
Def6+	13	0	PPV	100.00%
Def6-	1	236	NPV	99.58%
	14	236	Accuracy	99.60%
	250			

*analysis affected by unavailable data in the EHR for this field so modified criteria (Definition 1) was used

Table S5. PPV, NPV, Sensitivity and Specificity by FH Category.

Broken Down by Groups and Over All							
Unlikely+	Unlikely+	118	0			Sensitivity	95.16%
	Unlikely-	6	126			Specificity	100.00%
		124	126	250		PPV	100.00%
						NPV	95.45%
						Accuracy	97.60%
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Possible+	Possible+	110	1			Sensitivity	100.00%
	Possible-	0	139			Specificity	99.29%
		110	140	250		PPV	99.10%
						NPV	100.00%
						Accuracy	99.60%
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Probable+	Probable+	13	0			Sensitivity	100.00%
	Probable-	0	237			Specificity	100.00%
		13	237	250		PPV	100.00%
						NPV	100.00%
						Accuracy	100.00%
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Definitive+	Definitive+	2	0			Sensitivity	100.00%
	Definitive-	0	248			Specificity	100.00%
		2	248	250		PPV	100.00%
						NPV	100.00%
						Accuracy	100.00%
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FH All+	FH All+	125	1			Sensitivity	95.42%
	FH All-	6	118			Specificity	99.16%
		131	119	250		PPV	99.21%
						NPV	95.16%
						Accuracy	97.20%

Table S7. International Classification of Disease-9 codes used to identify the outcomes.

Diagnosis	ICD 9 Codes
Myocardial Infarction	410.00, 410.0, 410.01, 410.02, 410.1, 410.10, 410.11, 410.12, 410.20, 410.2, 410.21, 410.22, 410.30, 410.31, 410.32, 410.40, 410.4, 410.41, 410.42, 410.50, 410.51, 410.52, 410.60, 410.61, 410.62, 410.7, 410.70, 410.71, 410.72, 410.8, 410.80, 410.81, 410.82, 410.9, 410.90, 410.91, 410.92, 411.0, 412, 429.7, 429.71, 429.79
Heart Failure	398.91, 428.0, 428, 428.1, 428.20, 428.2, 428.21, 428.22, 428.23, 428.3, 428.30, 428.31, 428.32, 428.33, 428.40, 428.4, 428.41, 428.42, 428.43, 428.9
Ischemic Stroke	433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91
PCI	00.66, 17.55, 36.02, 36.03, 36.04, 36.05, 36.06, 36.07, 36.09, 36.01, C9600, C9601, C9602, C9604, C9605, C9606, C9607, G0290
CABG	36.10, 36.11, 36.12, 36.13, 36.14, 36.15, 36.16, 36.19
ICD	89.49, 37.94, 37.95, 37.96, 37.97, 37.98, C1721, C1722, C1777, C1882, C1895, C1896

Table S8. Cost Analysis -DEFINITIVE and PROBABLE categories combined as FH and compared to UNLIKELY (POSSIBLE excluded).

	FH		Non-FH		P-value
	Median	IQR	Median	IQR	
Total adjusted Revenue (2005-2015)	16425	41595	11153	30844	<0.0001
	FH		Non-FH		
Med Net Revenue	Median	IQR	Median	IQR	p-value
2014	1007	2586	860	2152	<0.0001
2015	1065	2709	850	2123	<0.0001

Table S9. Cost Analysis - DEFINITIVE and PROBABLE combined as FH and compared to UNLIKELY and POSSIBLE (combined as Non-FH).

	FH		Non-FH		P-value
	Median	IQR	Median	IQR	
Total adjusted Revenue (2005-2015)	16425	41595	11252	31198	<0.0001
	FH		Non-FH		
Med Net Revenue	Median	IQR	Median	IQR	p-value
2014	1007	2586	864	2171	<0.0001
2015	1065	2709	854	2141	<0.0001