Diagnosing Familial Hypercholesterolemia (FH) in the US: Results From the CASCADE FH Patient Registry

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Background

Familial hypercholesterolemia (FH):
- Autosomal dominant disorder
- Worldwide prevalence as high as 1:200
- Life-long elevations in low-density-lipoprotein cholesterol (LDL-C) lead to a 20-fold increased risk of premature coronary heart disease (CHD)

Three criteria can be used to diagnose FH
- Simon-Broome (Table 1)
- Dutch Lipid Clinic Network (DLCN,Table 2)
- United States (US) Make Early Diagnosis to Prevent Early Deaths (MEDPED,Table 3)

An estimated 1.5 million individuals in the US are affected by FH, yet **fewer than 10% of cases** are recognized.

The low US FH detection rate may be due to several issues:
- Lack of awareness of FH in the general community as well as among health care providers
- Lack of ICD-9 code for FH
- Unclear diagnostic practices in the US

To explore the issue of US FH diagnostic practices, we queried CASCADE-FH, the only active multi-center US FH patient registry.

Objective

To describe the diagnostic criteria used by lipid specialists (participating in the CASCADE-FH Registry) to diagnose FH in the US.

FH Diagnostic Criteria

Table 1. Simon Broome Criteria

Lipid levels (mg/dL) to be used as diagnostic criteria	
	Total Cholesterol > 290, or
	LDL-C > 190
Definite FH:	xanthomas in proband or family member or genetic confirmation
Probable FH:	premature CHD or pre-treatment hypercholesterolemia in 1st degree relative

Table 2. Dutch Lipid Clinic Network Criteria (DLCN)*

		Score
Family history		
1st degree relative with premature CHD, or LDL-C > 95th %ile		1
1st degree relative with xanthoma or arcus, or children with LDL-C > 95th %ile		2
Clinical history		
Patient with premature CHD		2
Patient with premature cerebral or peripheral vascular disease		1
Physical examination		
Xanthoma		6
Arcus prior to age 45 years		4
LDL-cholesterol (mg/dL)		
	LDL-C ≥330	8
	LDL-C 250–329	5
	LDL-C 190–249	3
	LDL-C 155–189	1
Functional mutation in *LDLR*, *APOB* or *PCSK9*		8

*Stratification: Definite FH: total score ≥ 8; Probable FH: 6-7; Possible FH: 3-5; Unlikely FH: < 3

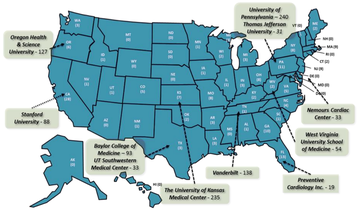
Table 3. Make Early Diagnosis to Prevent Early Death (MEDPED)

	Total Cholesterol (LDL-C) levels in mg/dL			
Age	1st degree relative	2nd degree relative	3rd degree relative	General Population
<18	220 (155)	230 (165)	240 (170)	270 (200)
20	240 (170)	250 (180)	260 (185)	290 (220)
30	270 (190)	280 (200)	290 (210)	340 (240)
40 +	290 (205)	300 (215)	310 (225)	360 (260)

The CASCADE-FH Patient Registry

In 2013, the FH Foundation (a nonprofit research advocacy organization) created the CAscade SCreening for Awareness and DEtection (CASCADE) FH Registry

Figure 1: CASCADE-FH Active clinical sites (n = 11) and number of patients enrolled per site (as of Nov 2014)



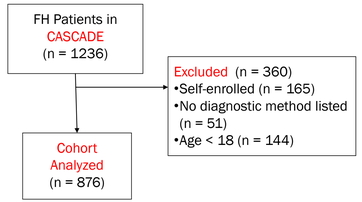
- CASCADE-FH Registry is a national initiative to increase FH awareness, characterize trends in treatment, and monitor clinical and patient-reported outcomes.
- CASCADE-FH Registry represents a collaboration between individuals affected with FH and clinical researchers to address gaps in knowledge with regard to FH screening, identification, and treatment.
- Registry participants enroll by either:
  1. Enrollment by a provider in a specialized lipid clinic
  2. Self-enrollment via an online portal for participants meeting pre-specified LDL-C criteria.
- As of May 2015, 16 sites are active

Methods

CASCADE-FH Registry was queried for the "diagnostic criteria" reported for each heterozygous or homozygous FH (n = 15) patient entered (Figure 2) by November 2014.

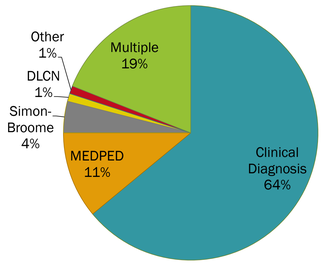
Diagnostic criteria were divided into 5 non-exclusive categories: 1) "clinical diagnosis," 2) MEDPED, 3) Simon-Broome, 4) DLCN, 5) other.

Figure 2: Flow diagram of cohort analyzed



Results

Figure 3. Diagnostic criteria reported in CASCADE-FH. DLCN denotes Dutch Lipid Clinic Network; MEDPED Make Early Diagnosis Prevent Early Death



Results (continued)

Table 4. Baseline Characteristics of Adult FH Patients in CASCADE-FH

	n = 876 US FH Patients
Age at enrollment (yrs)	53 (17)
Age at FH Diagnosis (yrs)	43 (18)
Female	57%
BMI (kg/m2)	28 (6)
Ethnicity/Race	78% white, 6% black, 3% Hispanic
Pretreatment Lipids*	
Total Cholesterol (mg/dL)	362 (104)
LDL-C (mg/dL)	269 (87)
Prior CAD	38%
Family history of MI	45%
Tendon Xanthomas	18%

* Pretreatment data available on n = 444 at time of abstract submission
Data shown as mean (SD) unless otherwise indicated
CAD denotes coronary artery disease; MI myocardial infarction

Table 5. Characteristics of Adult FH Patients in CASCADE-FH diagnosed via "Clinical Diagnosis" vs Established Criteria

	Clinical Diagnosis (n = 560)	MEDPED + DLCN + Simon Broome (n = 144)
Age (yrs)	55 (17)	47 (18)***
Female	55%	69%**
BMI (kg/m2)	28 (5)	29 (7)
Age at FH diagnosis (yrs)	45 (18)	37 (19)***
Prior CAD	41%	24%***
Family history of MI	44%	52%
Tendon Xanthomas	7%	19%***
Pre-treatment LDL-C (mg/dL)	254 (73) n = 243	278 (101) * n = 112

* p < 0.05; ** p < 0.01; ***p < 0.001
Data shown as mean (SD) unless otherwise indicated
BMI body mass index, CAD coronary artery disease, MI myocardial infarction

Discussion

Among US lipid clinics participating in the CASCADE-FH registry, most did not report utilizing one of the existing diagnostic tools.

Several factors may explain our findings:
- Lack of a consensus FH criteria in US
- Reliance on clinical diagnosis in older patients with CAD (Table 5)
- Data capture or entry bias (e.g. study coordinators may select "clinical diagnosis" by default).

Consistent application of diagnostic criteria would improve patient outcomes. In the Netherlands the DLCN criteria was a critical component of a public health strategy to identify FH patients for genetic testing and early treatment for CHD prevention. Application of these criteria resulted in identification of 71% of estimated cases.

Several limitations merit discussion:
- Cross sectional analysis
- Data reflects specialty lipid centers, mostly academic centers, and may not reflect practice in primary care.
- Genetic confirmation of FH was not systematically performed
- "Clinical diagnosis" was not defined and does not preclude the use of existing diagnostic criteria

Conclusions

Established FH criteria are not regularly utilized to diagnose FH in the US. A need exists to develop a consensus definition to better identify FH patients, appropriately treat with lipid lowering agents , and ultimately prevent CHD events.

The Cascade FH Registry is an initiative of the FH Foundation.

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