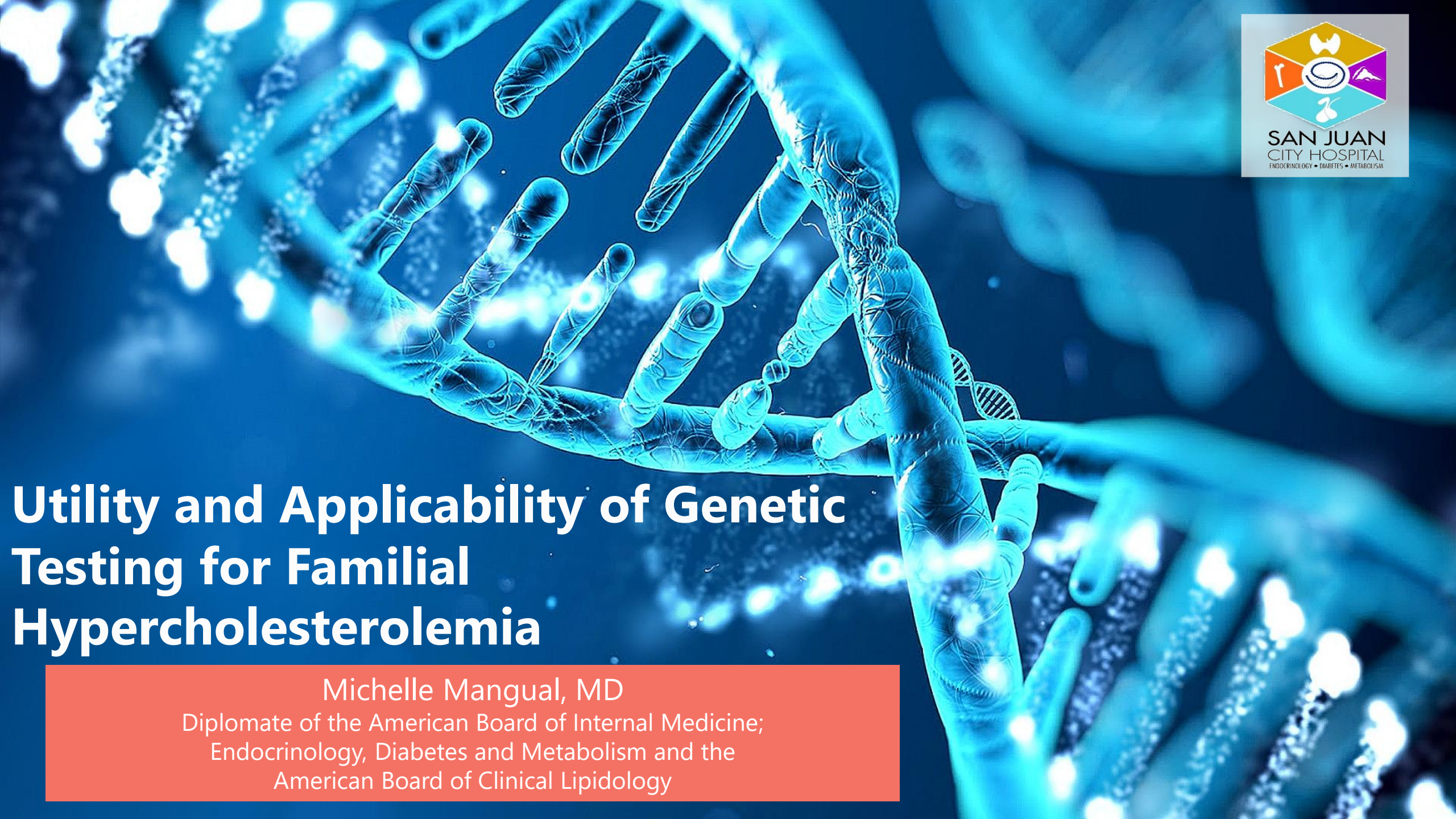


Utility and Applicability of Genetic Testing for Familial Hypercholesterolemia

Michelle Mangual, MD

Diplomate of the American Board of Internal Medicine;
Endocrinology, Diabetes and Metabolism and the
American Board of Clinical Lipidology

The Power of Genetic Testing
An example from My Code

- 62-year-old woman
- Struggle to control high cholesterol for years.
- Learned she has LDLR pathogenic variant (c.1775G>A, p.Gly592Glu) via My Code.
- Prompted her to pay attention to her chest pain.
- Sought medical attention, diagnosed with CAD, underwent triple CABG.
- Several relatives now tested and confirmed to also have FH.

mycode

The New York Times

October 3, 2017

"If I had not taken that test, I might be dead by now"

Learning Objectives

- To briefly discuss the Pathogenesis of Familial Hypercholesterolemia (FH)
- To analyze the phenotypical spectrum of FH and the rational for genetic testing.
- To review the consensus statement on the clinical utility for genetic testing in FH.
- To show some evidence on the acceptability and accessibility of genetic testing.
- Genetic counseling and resources for patients.

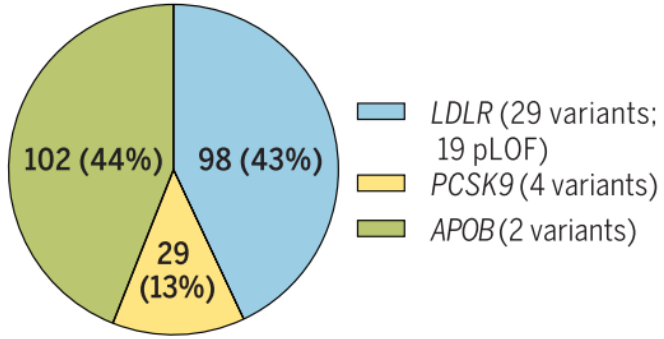
FH FOUNDATION
Raising Awareness. Saving Lives.

FH is the Most Common Genetic Cause of CV Disease

- Estimated prevalence of ~1:220.[1]
  - 1:100 in French Canadians and Dutch Afrikaners
- Approximately 1 million patients in the US and 30 million affected individuals worldwide
  - >90% remains undiagnosed.
- Recent data suggests a prevalence of molecularly defined HoFH to be ~1 in 200,000 to 300,000 persons.[2]

A

Distribution of 229 heterozygous carriers by FH gene



B

Population characteristics	FH variant positive/total	Estimated prevalence
All DiscovEHR participants	229/50,726	1:222
Participants recruited from cardiac catheterization lab	57/6,747	1:118
Participants recruited from other sites	172/43,979	1:256

1. Abul-Husn et al., Science 354, 2016
2. Sjouke B, et al. Curr Opin Lipidol 2015;26:200–9

Table 1 Characteristics of studies included in systematic review of FH prevalence

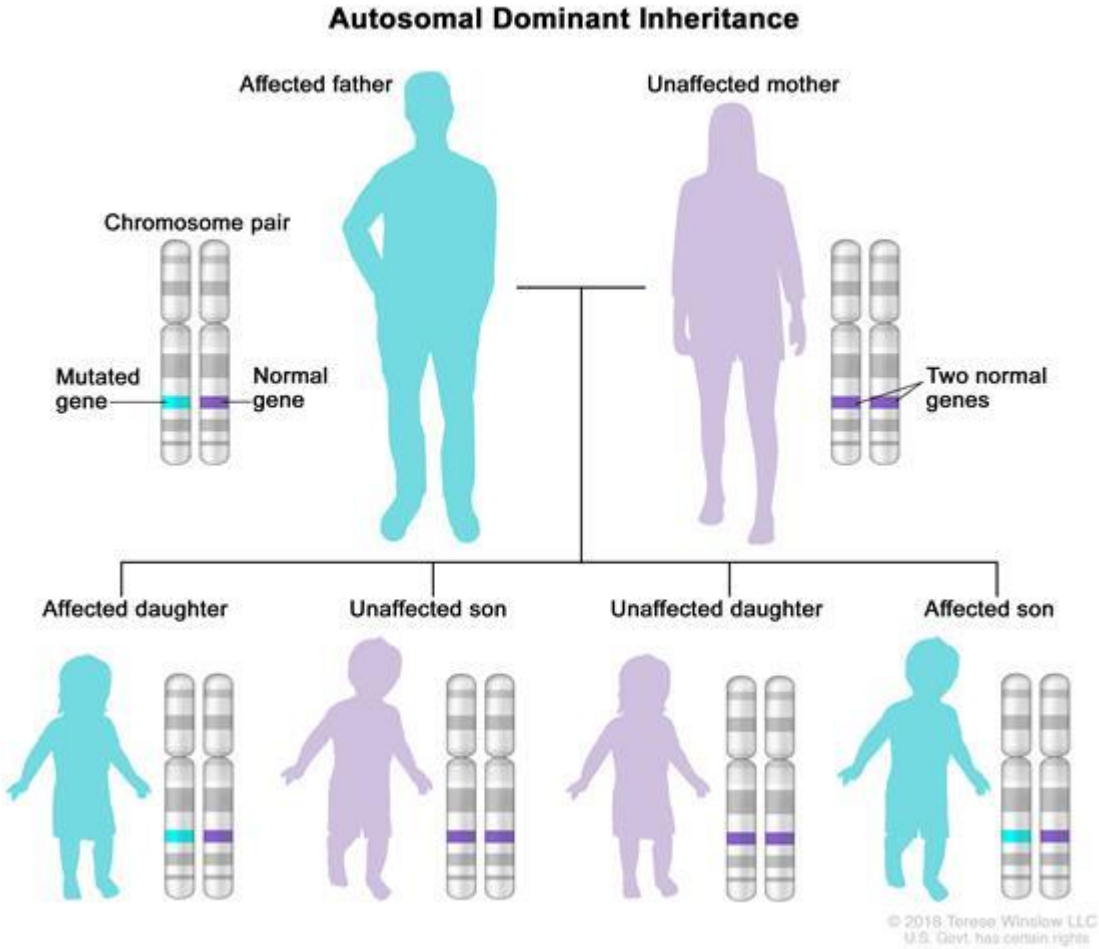
Study author (publication year)	Country	Data source(s)	Enrolment period (years)	Diagnostic criteria	Sample size	Age (years)	Female, N (%)	FH cases, N	Prevalence estimate (95% CI)*	Study quality
Studies reporting on FH prevalence in adults										
Abdul-Husn *et al* (2016)[54]	USA	Geisinger Health System EHR	NR	DNA	50726	18+	30334 (59.8%)	229	0.45% (0.40% to 0.51%)	★★★
Benn *et al* (2012)[11]	Denmark	Copenhagen General Population Study	2003+	DLCN	69016	20–100	37959 (55.0%)	502	0.73% (0.67% to 0.79%)	★★★
				DNA	60710			20	0.03% (0.02% to 0.04%)	
				SBR	69016			2830	4.10% (3.95% to 4.25%)	
				MEDPED	69016			552	0.80% (0.73% to 0.87%)	
Benn *et al* (2016)[52]	Denmark	Copenhagen General Population Study	2003+	DLCN	98098	20–100	53958 (55.0%)	341	0.35% (0.31% to 0.39%)	★★★
				DNA	98098			174	0.18% (0.15% to 0.20%)	
				SBR	98000			3905	3.98% (3.86% to 4.11%)	
				MEDPED	93398			789	0.84% (0.79% to 0.90%)	
Catapano *et al* (2016)[42]	Multinational study†	DYSIS	2008–2013	DLCN	54811	45+	24884 (45.5%)	656	1.20% (1.11% to 1.29%)	★★
de Ferranti *et al* (2016)[43]	USA	NHANES	1999–2012	DLCN	36949	20+	18991 (51.4%)	146	0.40% (0.33% to 0.46%)	★★★
Guglielmi *et al* (2016)[55]	Italy	Health Longitudinal Patient Database	NR	DLCN	1135000	15+	NR	2043	0.18% (0.17% to 0.19%)	★★★
Kalina *et al* (2001)[6]	Hungary	Family doctors' registers	1996–1998	MEDPED	21000	NR	NR	39	0.19% (0.13% to 0.25%)	★★★
Khera *et al* (2016)[10]	Multinational study‡	MiGen Consortium CHARGE Consortium	NR	DNA	20485	NR	3696 (26.2%)	24	0.12% (0.07% to 0.17%)	★★
				LDL-C				1386	6.77% (6.43% to 7.11%)	
Lahtinen *et al* (2015)[46]	Finland	FINRISK Cohort	1992, 1997, 2002	DNA	28465	25–74	14501 (50.9%)	35	0.12% (0.09% to 0.17%)	★★★
		Health 2000 Cohort	2000–2001			30+				
Neil *et al* (2000)[7]	United Kingdom	Simon Broome Register	1980–1999	SBR	456550	20+	231796 (50.8%)	320	0.07% (0.06% to 0.08%)	★★
Pajak *et al* (2016)[44]	Poland	POL-MONICA Krakow	1983–1984 1987–1988 1992–1993	DLCN	37889	35–64	NR	153	0.40% (0.34% to 0.47%)	★★★
		POL-MONICA Warszawa	1984 1988 1993			35–64				
		WOBASZ	2003–2004			20–74				
		Pilot HAPIEE	2001–2002			45–64				
		HAPIEE	2003–2005			45–70				
		NATPOL 2011	2011			20–74				

Table 1 Continued

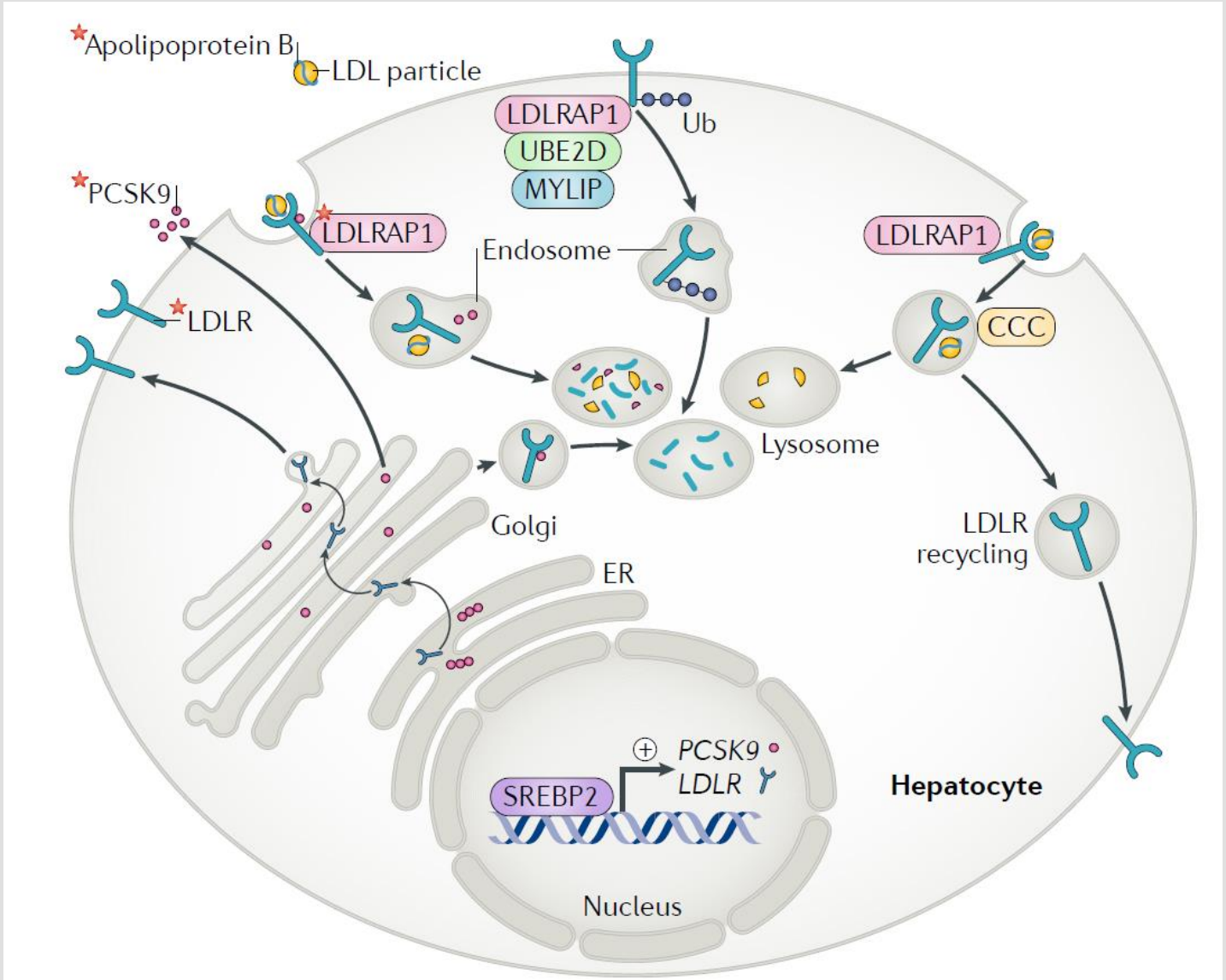
Study author (publication year)	Country	Data source(s)	Enrolment period (years)	Diagnostic criteria	Sample size	Age (years)	Female, N (%)	FH cases, N	Prevalence estimate (95% CI)*	Study quality
Perak *et al* (2016)[49]	USA	FHS	1948	LDL-C	68565	30–62	19693 (41.0%)	3850	5.62% (5.44% to 5.79%)	★★
		FOS	1971			5–70				
		CARDIA	1985–1986			18–30				
		ARIC	1987–1989			45–64				
		NHANES III—Mortality	1988–1994			17–90				
		CHS	1989–1990			65+				
Safarova *et al* (2016)[56]	USA	Mayo ECH	1993–2014	DLCN	131000	18+	77290 (59.0%)	423	0.32% (0.29% to 0.35%)	★★★
Shi *et al* (2014)[53]	China	Jiangsu Nutrition Study	2007	DLCN	9324	20+	5356 (57.4%)	26	0.28% (0.18% to 0.40%)	★★★
				LDL-C	9280			44	0.47% (0.34% to 0.62%)	
Steyn *et al* (1996)[47]	South Africa	Random sample from south-western Cape	NR	DNA	1612	15–64	809 (50.2%)	18	1.12% (0.66% to 1.69%)	★★
Vickery *et al* (2016)[57]	Australia	General practitioners' offices in Perth	NR	DLCN	157290	18–70	NR	782	0.050% (0.46% to 0.53%)	★★★
Vuorio *et al* (1997)[48]	Finland	Outpatient lipid clinic of North Karelia, Joensuu	1992–1996	DNA	180000	NR	NR	407	0.23% (0.20% to 0.25%)	★★★
Watts *et al* (2015)[45]	Australia	AusDiab	1999–2000	DLCN	18222	NR	NR	81	0.44% (0.35% to 0.55%)	★★
		Baker IDI	2005–2012							
Studies reporting on FH prevalence in children										
de Ferranti *et al* (2016)[43]	USA	NHANES	1999–2012	DLCN	13343	12–19	NR	146	0.42% (0.32% to 0.54%)	★★★
Pang *et al* (2016)[51]	Australia	Western Australia Pregnancy Cohort Study	1989–1991	LDL-C	2868	14/17	770 (48.1%)	6	0.37% (0.12% to 0.74%)	★
Wald *et al* (2016)[58]	United Kingdom	General Medical Practices	2012–2015	DNA	10095	12.4–13.3 months	4882 (48.4%)	28	0.28% (0.18% to 0.39%)	★★★
Yang *et al* (2012)[50]	Korea	KNHANES IV	2007–2009	LDL-C	2363	10–18	1118 (47.3%)	9	0.38% (0.17% to 0.68%)	★★

Inheritance Pattern

- Is an autosomal dominant trait with complete penetrance.
- HeFH is caused by a single pathogenic variant in LDLR, ApoB or PCSK9 genes.
- Compound HeFH is caused by 2 different pathogenic variants in different alleles.
- HoFH is caused by biallelic pathogenic variants.
- There is a gene dosage effect.



LDL Receptor Life Cycle



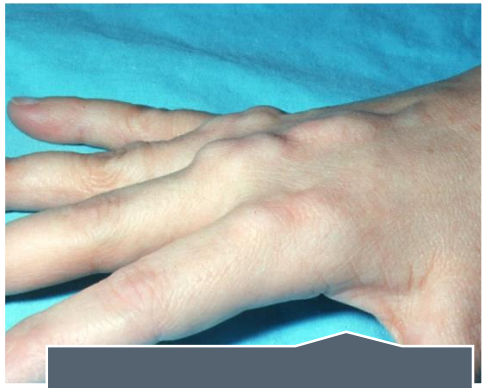
Berberich and Hegele. Nature Reviews Cardiology. 2018

Major and Minor Monogenic Determinants of FH

Gene	Inheritance pattern	OMIM number	Proportion of patients with monogenic FH (%)	Mutation types	Refs
Major determinants					
LDLR	Autosomal co-dominant	606945	80–85	Splicing, frameshift, copy number variation, nonsense, and missense	1,2
APOB	Autosomal co-dominant	107730	5–10	Frameshift, missense, nonsense, and splicing	1,2
PCSK9	Autosomal co-dominant	607786	<1	Frameshift and missense	1,2
LDLRAP1	Autosomal recessive	605747	<1	Frameshift, missense, and nonsense	1,10
Minor determinants					
APOE	Autosomal dominant	107741	<<1	Missense	53
STAP1	Autosomal dominant	604298	<<1	Missense	54
LIPA	Autosomal recessive	613497	<<1	Frameshift	56
ABCG5	Autosomal recessive	605459	<1	Nonsense	55
ABCG8	Autosomal recessive	605460	<<1	Unproven (only by analogy with *ABCG5*)	55

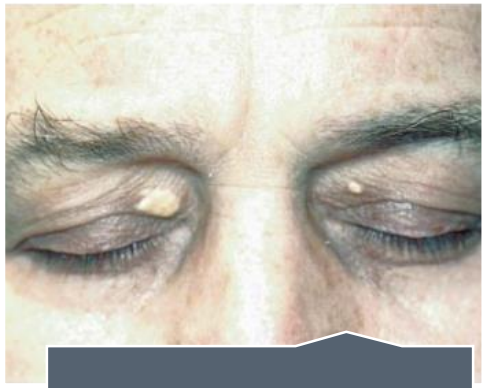
Berberich and Hegele. Nature Reviews Cardiology. 2018

Physical Findings in FH

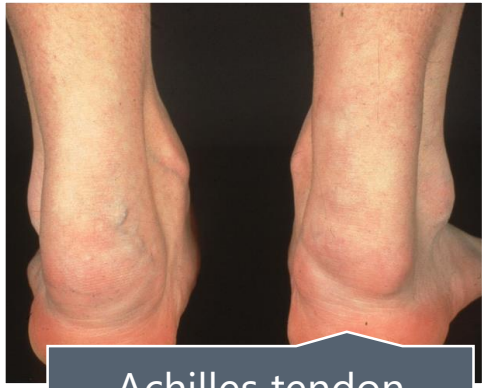


Tendon xanthomas

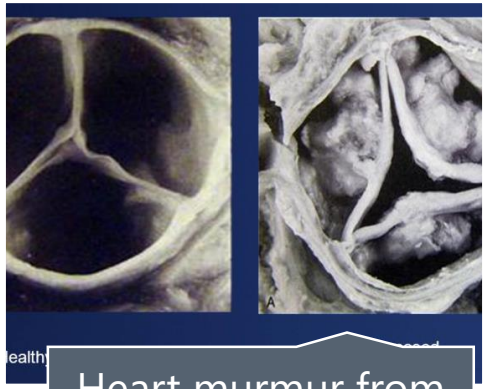
Corneal arcus



Xanthelasma

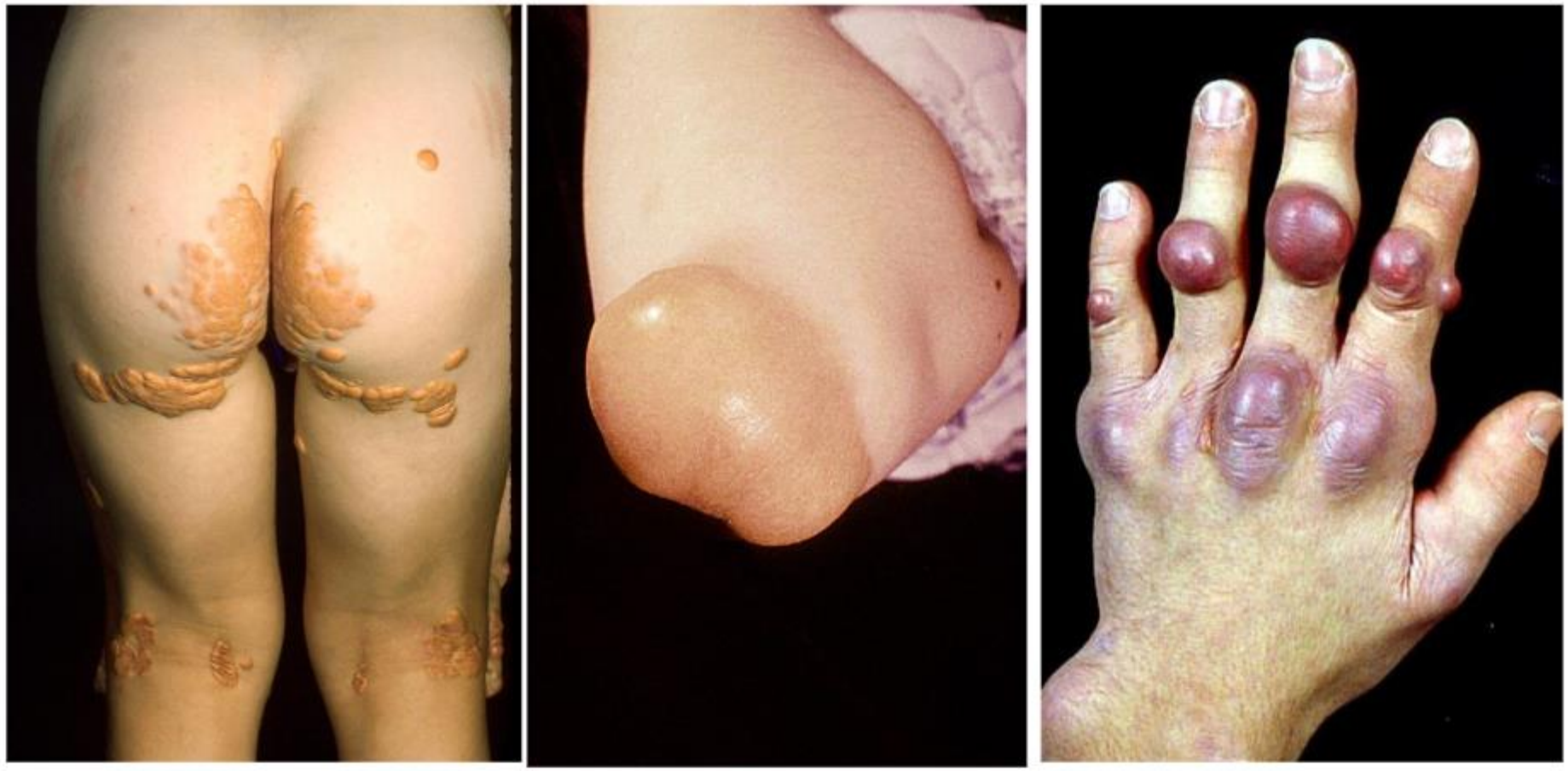


Achilles tendon xanthomas



Heart murmur from AV stenosis

Physical Findings in Homozygous FH



5-year old

17-year old

21-year old

DAVIGNON 2006

Table 1 | **Comparison between clinical scoring systems for FH**

Criteria	Simon Broome Register[18]	Dutch Lipid Clinic Network[19]	MED-PED[20a]	AHA[21]	Canadian Criteria[22,144]
Lipids					
Total cholesterol (mmol/l)	• >7.5 (adult) [a] >290 mg/dl • >6.7 (child) [a] >259	NA	NA	NA	NA
LDL cholesterol (mmol/l)	• >4.9 (adult) [a] >189 • >4.0 (child) [a] >155	• >8.5 [8] >325 mg/dl • 6.5–8.4 [5] 251-325 • 5.0–6.4 [3] 191-250 • 4.0–4.9 [1] 155-190	>5.7–9.3[b]	• >5.0 (adult) [a] • >4.0 (child) [a]	• >4.0 (child) [a] • >4.5 (18–39 years) [a] • >5.0 (>40 years) [a] • >8.5 [b]
Physical stigmata					
Personal	Tendon xanthoma [b]	• Tendon xanthoma [6] • Arcus cornealis[c] [4]	NA	NA	Tendon xanthoma [c]
Family	Tendon xanthoma in one relative [b]	Tendon xanthoma or arcus cornealis [2]	NA	NA	NA
Family history					
CAD	MI aged <50 years in two relatives or aged <60 years in one relative [d]	• Premature CAD[d] [2] • Premature CVD or PVD[d] [1]	NA	Premature CAD in one relative [b]	Premature CAD in one relative[d] [d]
LDL cholesterol (mmol/l)	>7.5 in one or two relatives [e] >290	Child with LDL cholesterol >95th percentile [2]	NA	One affected relative [c]	One relative with high LDL-cholesterol level [d]
Genetics	NA	NA	Known FH in a relative	NA	FH mutation in one relative [c]
Genetics					
Genetic mutations	*APOB*, *LDLR*, or *PCSK9* mutation [c]	*APOB*, *LDLR*, or *PCSK9* mutation [8]	NA	*APOB*, *LDLR*, or *PCSK9* mutation [d]	*APOB*, *LDLR*, or *PCSK9* mutation [c]
Diagnosis					
Diagnosis of FH	• Definite: a + (b or c) • Probable: (a + d) or (a + e)	• Definite: >8 • Probable: 6–8 • Possible: 3–5	Meets adjusted LDL-cholesterol cut-off point	a + (b or c) or d	• Definite: (a + c) or b • Probable: a + d

CAD, coronary artery disease; CVD, cerebrovascular disease; FH, familial hypercholesterolaemia; MED-PED, Make Early Diagnosis — Prevent Early Death; MI, myocardial infarction; NA, not applicable; PVD, peripheral vascular disease. [a]Requires a diagnosis of FH in a family member. [b]Cut-off based on year and degree of separation from affected relative. [c]Arcus cornealis when aged <45 years. [d]Aged <55 years in men and aged <60 years in women.

Berberich and Hegele. Nature Reviews Cardiology. 2018

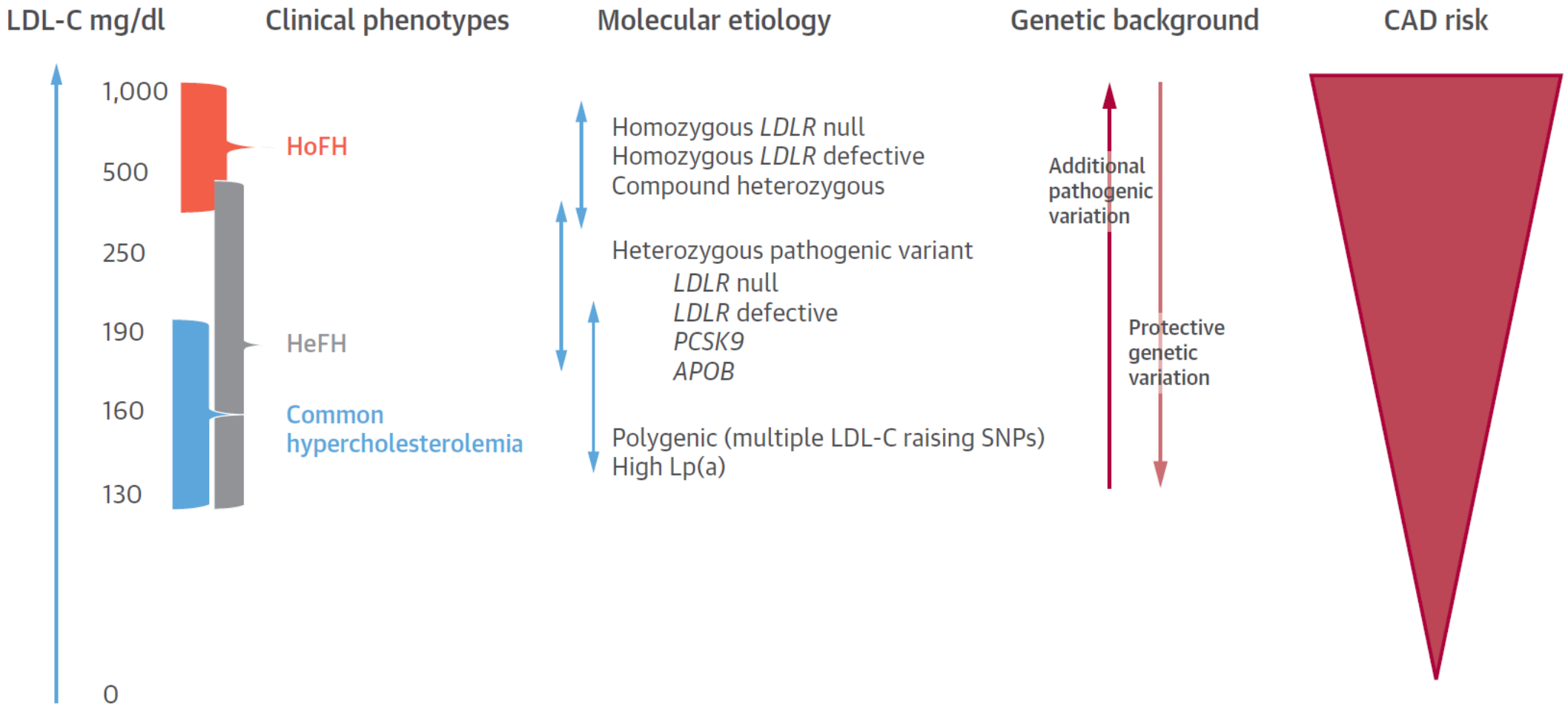
Table 4
The ability of the Simon Broome Register Group, MEDPED and Dutch Lipid Clinic Network criteria to predict the results of the molecular genetic analysis of the LDL receptor gene and of the apoB R3500 Q mutation

Clinical criteria		Sensitivity (%)	Mutation detection rate (%)	Specificity (%)[a]	1-Specificity (%)[a] = false positive rate
Simon Broome Register	Definite FH	34.1 (26.1–42.7) *35.9*	61.3 (49.4–72.4) *59.2*	89.4 (85.1–92.8)	10.6 (7.2–14.9)
	Definite or possible FH	90.4 (84.1–94.8) *93.2*	38.5 (33.1–44.1) *35.4*	28.6 (23.3–34.3)	71.4 (65.7–76.7)
MEDPED	Total cholesterol	63.4 (54.5–71.6) *69.0*	53.5 (45.4–61.6) *52.0*	73.4 (67.8–78.6)	26.6 (21.4–32.2)
	LDL-cholesterol	70.3 (61.2–78.4) *75.5*	51.6 (43.6–59.5) *49.7*	69.8 (63.8–75.3)	30.2 (24.7–36.2)
Dutch Lipid Clinic Network	Definite FH	41.5 (33.1–50.3) *42.7*	62.9 (52.0–72.9) *60.2*	87.9 (83.4–91.5)	12.1 (8.5–16.6)
	Definite or probable FH	66.7 (58.0–74.5) *68.3*	48.1 (40.8–55.5) *45.2*	64.5 (58.5–70.1)	35.5 (29.9–41.5)
	Definite, probable or possible FH	99.3 (95.9–100.0) *99.1*	34.3 (29.6–39.2) *31.1*	5.9 (3.4–9.3)	94.1 (90.7–96.6)

95% Confidence intervals are given in parentheses. Data concerning only LDLR mutation carriers are given in italics.

[a] Specificity and 1-specificity are the same for LDLR mutations only.

FIGURE 1 Phenotypic Spectrum of FH



Sturm, et al. JACC. V ol. 72 , N0 .6 , 2018

The Rationale for Genetic Testing

- Provides a definitive molecular diagnosis of FH.
- Provides prognostic and risk stratification information.
- Facilitates family-based cascade testing.
- Allows for precision during genetic counseling.
- Has value to the pediatric population with FH.
- Personal utility
- Minimal psychological impact.

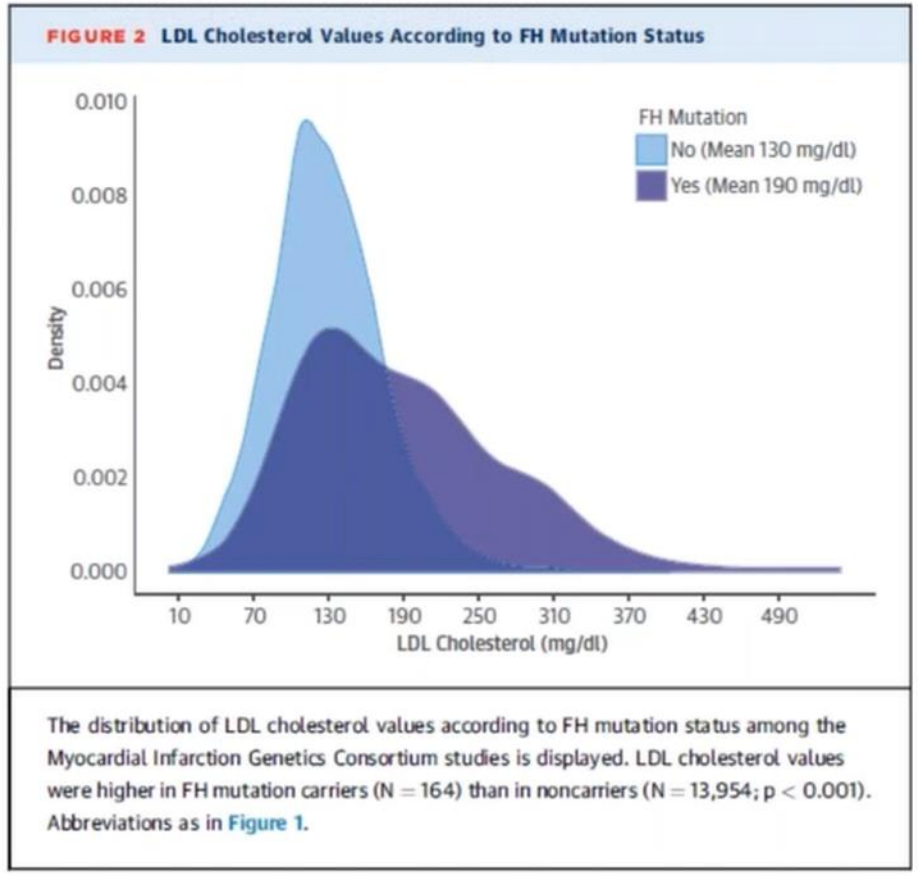
Limitations to diagnostic criteria in *absence of* DNA Testing

- Availability of statins and decreased saturated fat intake, have altered the “classic” FH clinical presentation.
- Physical exam findings and family history of premature CVD present in only a minority of molecularly defined FH in SAFEHEART Registry.
  - Xanthomas <15%
  - Corneal arcus ~ 20%
- Similar results in CASCADE FH Registry
- In a national screening program (Norway), only 8% of affected relatives had xanthomas and only 5% had xanthelasma at genetic testing.

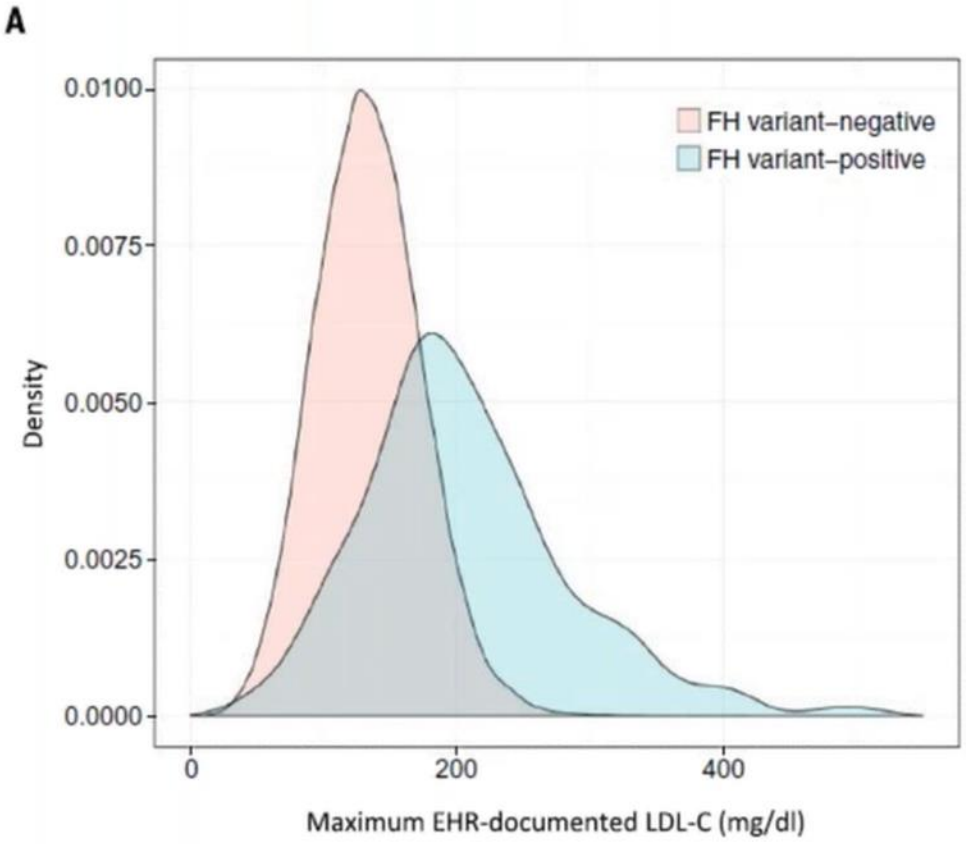
Limitations to family history in diagnosing FH

- Reduced penetrance
- Affected relatives on lipid-lowering therapy (LLT)
- Reduced clinical sensitivity and/or specificity of self-reported family history
- Unavailability of family history to some patients
- Of children with molecularly confirmed FH in Slovenial national universal lipid screening program, only 40.6% had a family history of CVD
- In the absence of molecular testing, there are limitations to diagnosing FH in children – DLNC are not valid in children, so diagnosis relies on family history and serial fasting LDL-C measurements

Overlapping LDL-C Levels: Genetic testing discriminates between those with and without an FH variant

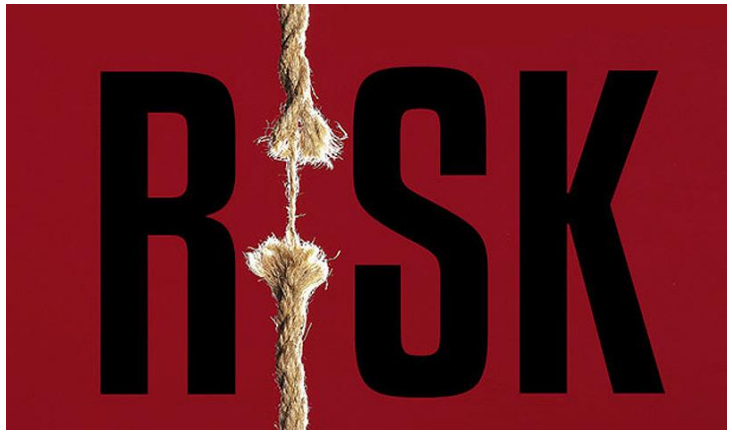


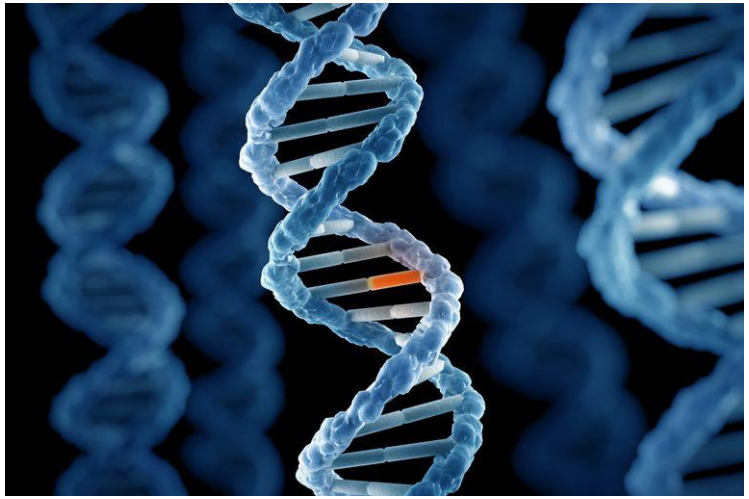
Khera et al *JACC* 2016

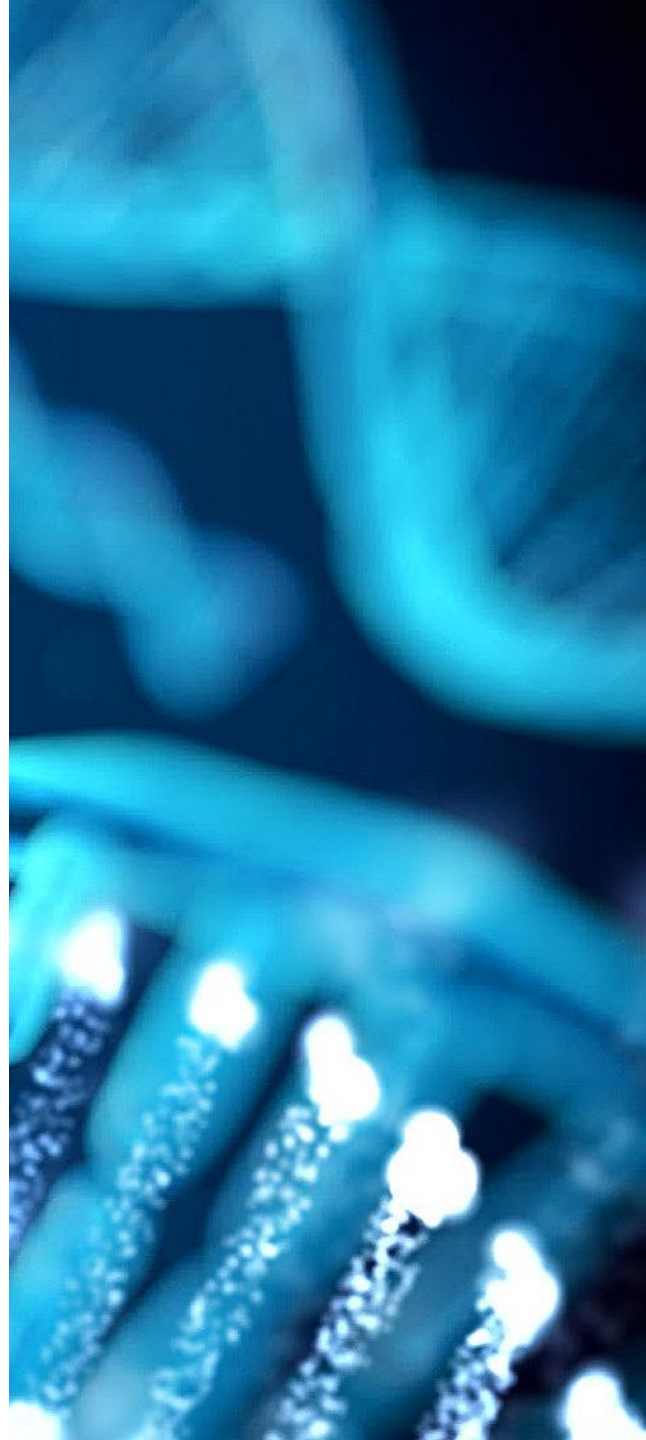


Abul-Husn et al *Science* 2016

The Presence of an FH Mutation Increases Risk







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Diagnostic Yield and Clinical Utility of Sequencing Familial Hypercholesterolemia Genes in Patients With Severe Hypercholesterolemia

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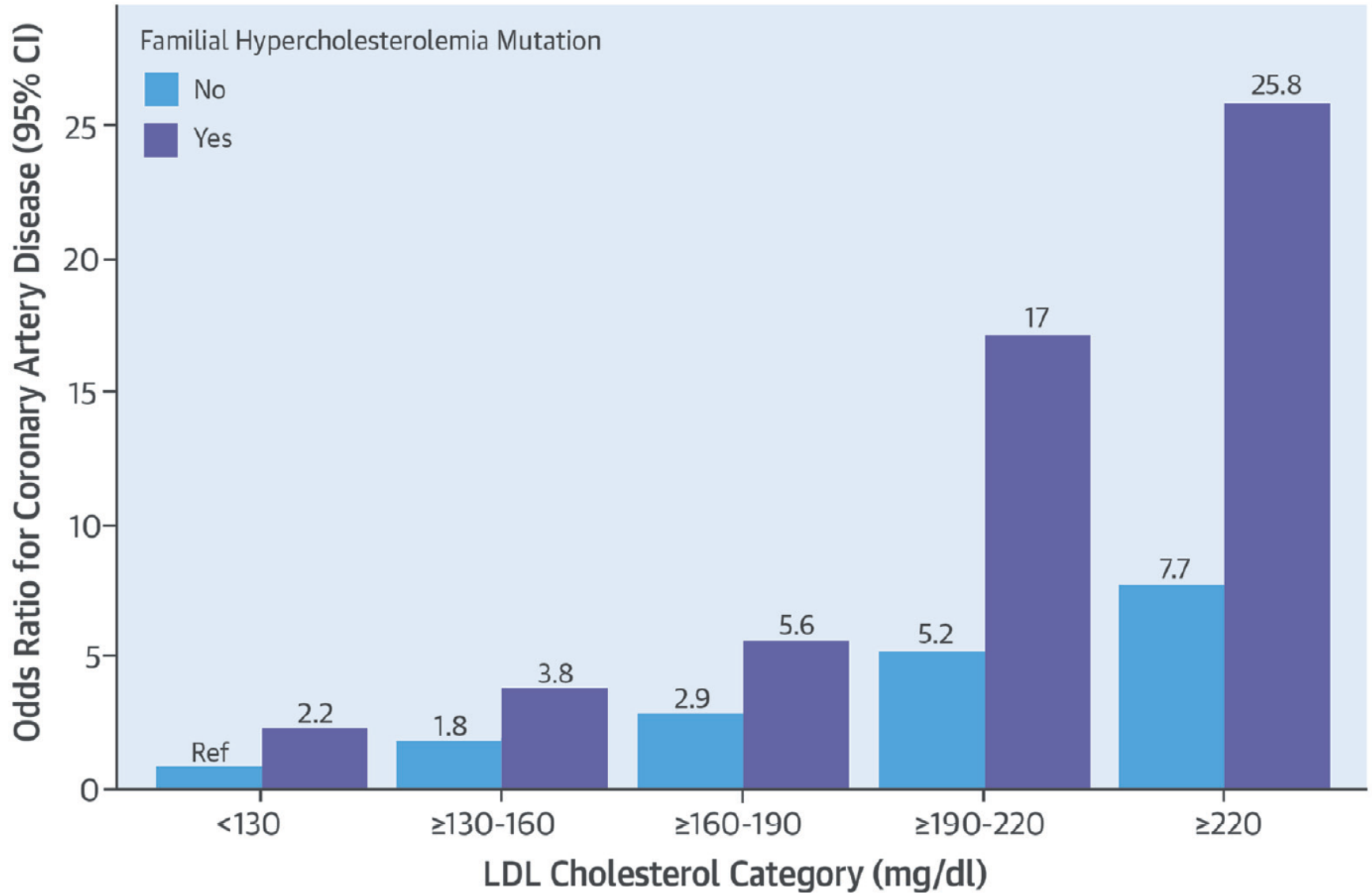
B. Impact of Familial Hypercholesterolemia Mutation Status on Coronary Artery Disease According to LDL Cholesterol Level



Khera, A.V. et al. J Am Coll Cardiol. 2016;67(22):2578-89.

European Heart Journal (2017) **38**, 1573–1579
doi:10.1093/eurheartj/ehx004

CLINICAL RESEARCH
Lipids

Impact of clinical signs and genetic diagnosis of familial hypercholesterolaemia on the prevalence of coronary artery disease in patients with severe hypercholesterolaemia

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FH Mutation with Clinical Signs = Highest Risk of CAD

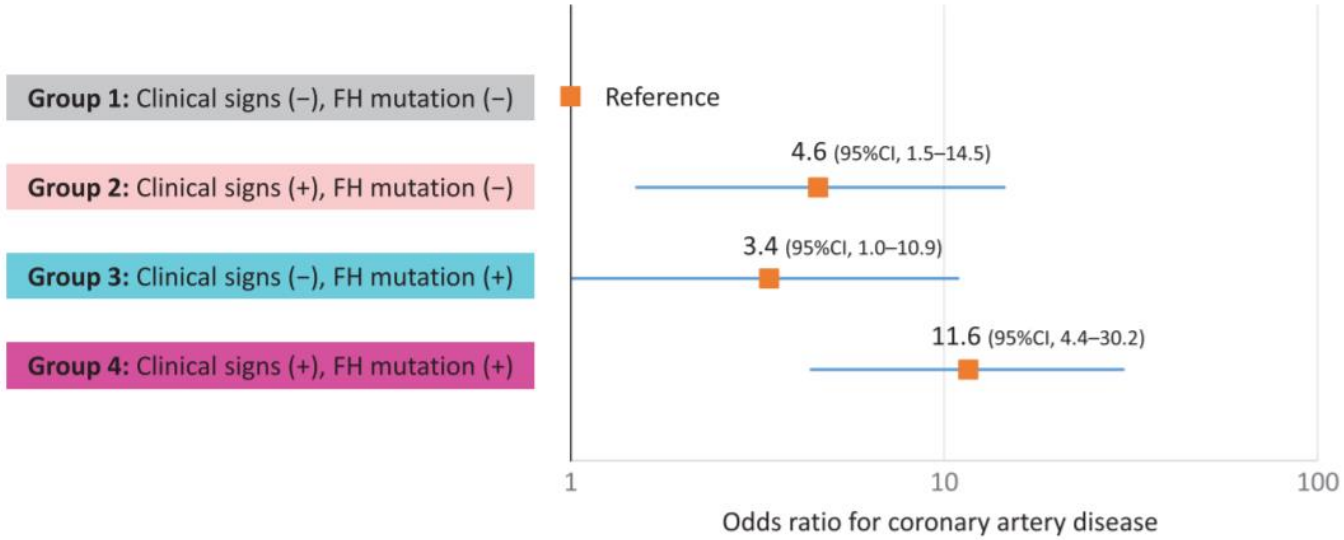


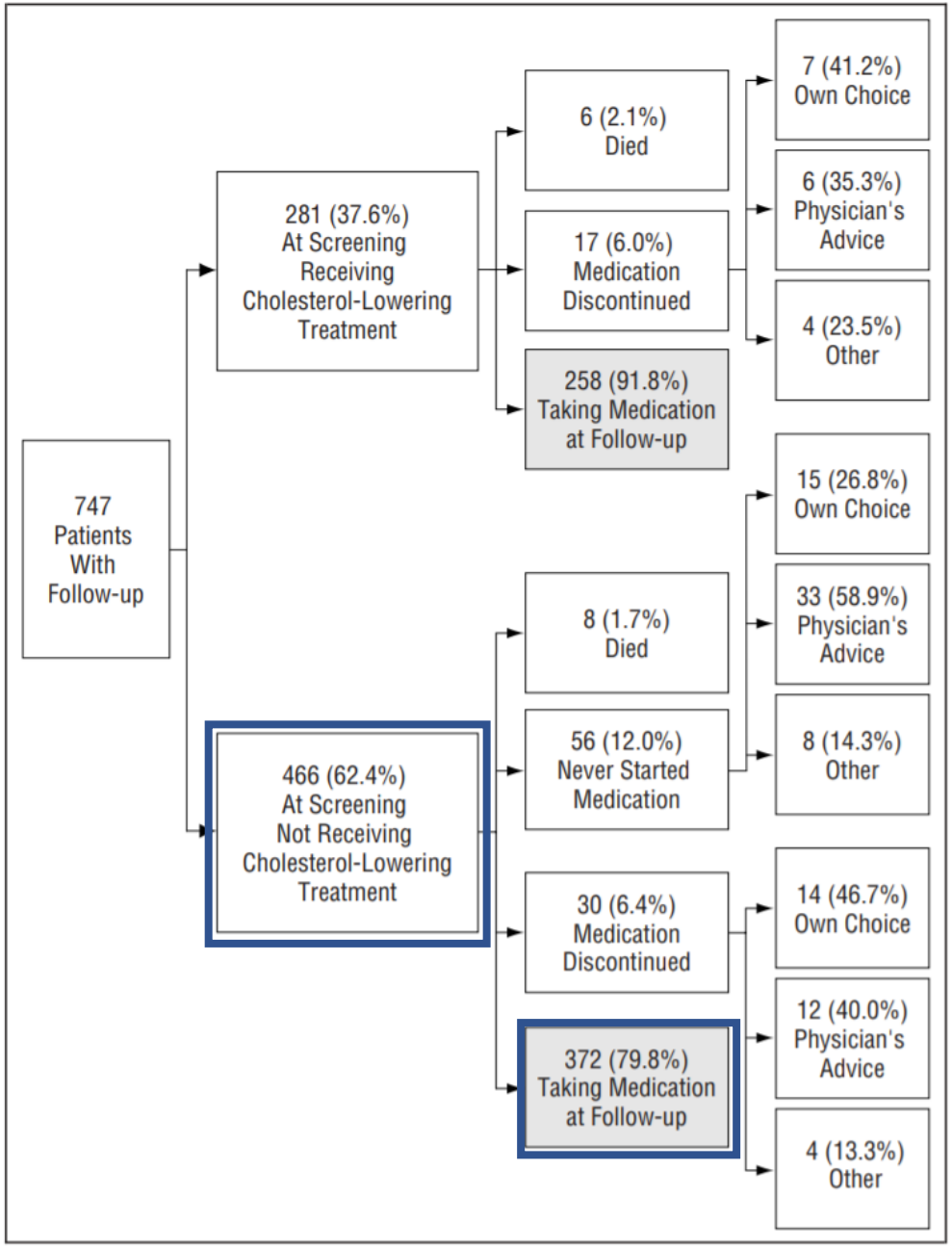
Figure 2 Impact of clinical signs and genetic diagnosis of familial hypercholesterolaemia on risk of coronary artery disease. Odds ratios were calculated using logistic regression after adjustment for age, sex, hypertension, diabetes, smoking, and low-density lipoprotein cholesterol levels. FH, familial hypercholesterolaemia; CAD, coronary artery disease; CI, confidence interval.

ORIGINAL INVESTIGATION

Long-term Compliance With Lipid-Lowering Medication After Genetic Screening for Familial Hypercholesterolemia

Marina A. W. Umans-Eckenhausen, MD; Joep C. Defesche, PhD; Marjel J. van Dam, MD; John J. P. Kastelein, MD, PhD

Arch Inter Med. 2003; 163:65-68.



Composition of the patient cohort studied and medication status of 747 patients with familial hypercholesterolemia after identification by DNA diagnosis. Because of rounding, percentages may not total 100.

Arch Inter Med. 2003; 163:65-68.

Cascade Testing

- CDC Tier 1 Genomics Application
  - Define as those having significant potential for positive impact on public health based on evidence-based guidelines and recommendations
- Imperative to identify all individuals in FH families
- Genetic cascade testing is superior to lipid cascade testing
  - Unambiguous cascade screening
- Can reduce average age of FH diagnosis
- Can increase % of individuals receiving LLT
- Is cost effective – 2017 systematic review confirms[1]
- Some labs are now doing this at no cost to the relative

Rosso et al. Ann Ig 2017

You don’t find one patient with FH…
You find families with FH

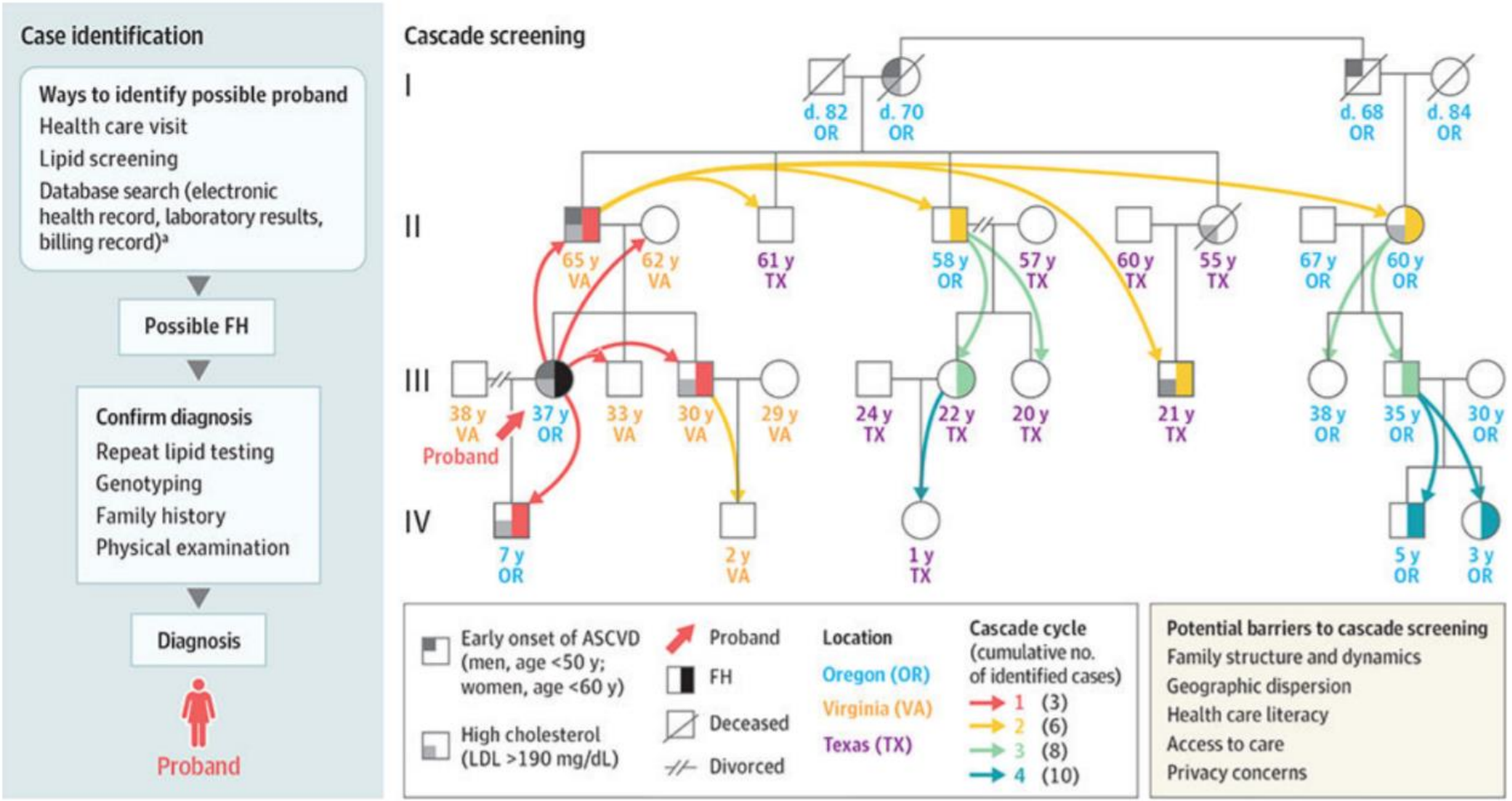


Figure. Process From Case Identification to Cascade Screening

Knowles. JAMA. 2017 July 25; 318(4): 381–382.

LDL alone Will Miss Affected Relatives

Table 5
Percentage of patients with LDL-cholesterol concentrations above the age- and sex-specific 90th or 95th percentile

	Index patients		Relatives	
	Mutation carriers ($n=135$)	Non-carriers ($n=273$)	Mutation carriers ($n=205$)	Non-carriers ($n=180$)
Patients with available LDL-cholesterol concentrations (%)	97.0	95.6	87.3	94.4
Patients with LDL-cholesterol > 95th percentile (%)	94.7	70.5	67.0	6.5
Patients with LDL-cholesterol > 90th percentile (%)	99.2	91.2	76.5	14.7

- 23% of mutation carriers had LDL-C <90th percentile
- 14.7% of non-carriers had LDL-C >90th percentile

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THE PRESENT AND FUTURE

JACC SCIENTIFIC EXPERT PANEL

Clinical Genetic Testing for Familial Hypercholesterolemia

JACC Scientific Expert Panel

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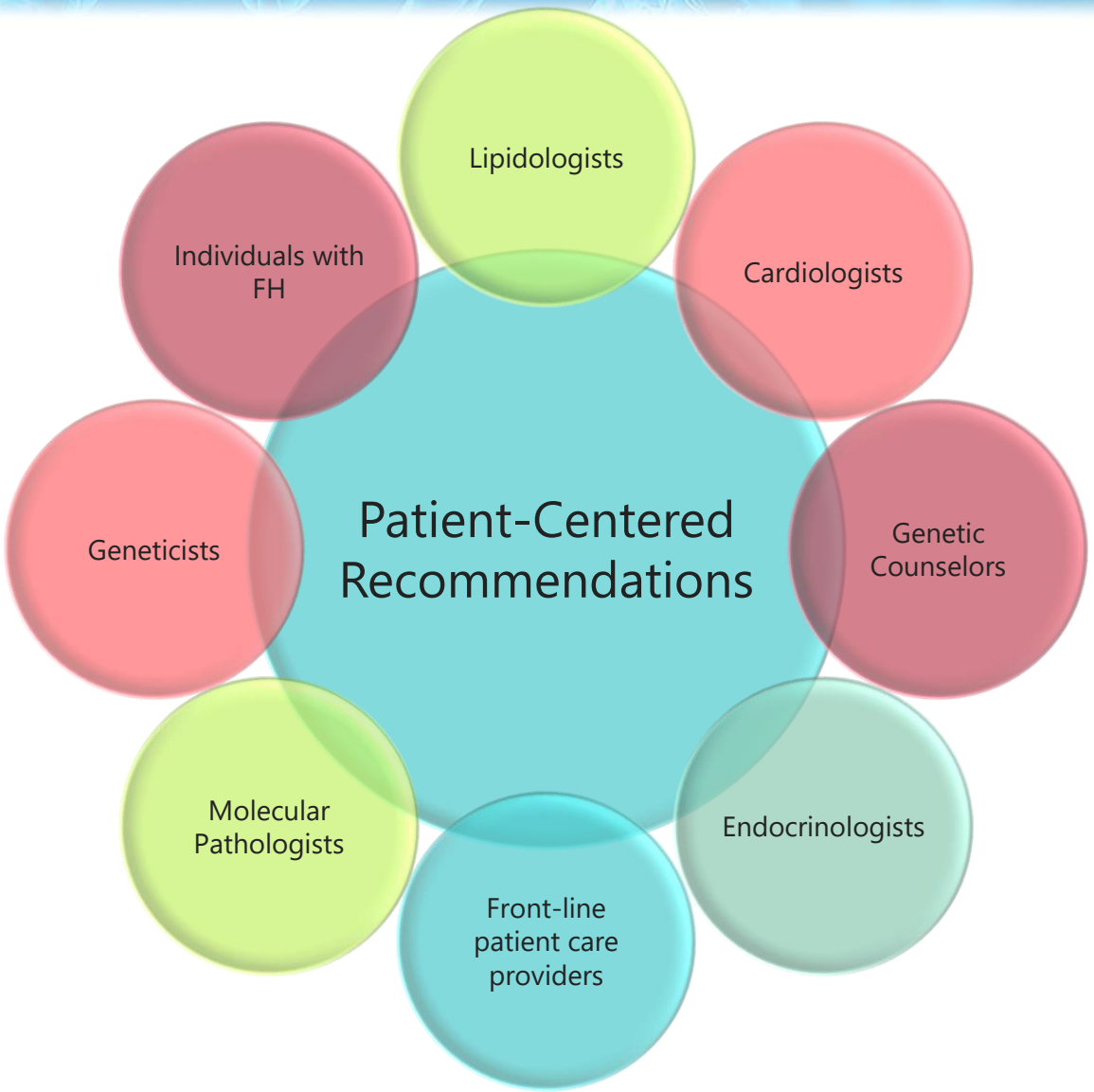
Convened by the Familial Hypercholesterolemia Foundation

International, Multi-Stakeholder Expert Panel



Who should we offer genetic testing to?

TABLE 2 Recommendations and Considerations for Genetic Testing for FH

A. Proband (index case)

Genetic testing for FH **should be offered** to individuals of any age in whom a strong clinical index of suspicion for FH exists based on examination of the patient's clinical and/or family histories. This index of suspicion includes the following:

1. Children with persistent* LDL-C levels ≥160 mg/dl or adults with persistent* LDL-C levels ≥190 mg/dl without an apparent secondary cause of hypercholesterolemia† and with at least 1 first-degree relative similarly affected or with premature CAD‡ or where family history is not available (e.g., adoption)
2. Children with persistent* LDL-C levels ≥190 mg/dl or adults with persistent* LDL-C levels ≥250 mg/dl without an apparent secondary cause of hypercholesterolemia,† even in the absence of a positive family history

Evidence Grade: Class of Recommendation IIa, Strength of Evidence B-NR

Should be ***offered***
Very intentional wording

Sturm, et al. JACC. V ol. 72 , N0 .6 , 2018

Additional Considerations for Probands

Genetic testing for FH **may be considered** in the following clinical scenarios:

1. Children with persistent* LDL-C levels ≥160 mg/dl (without an apparent secondary cause of hypercholesterolemia†) with an LDL-C level ≥190 mg/dl in at least 1 parent or a family history of hypercholesterolemia and premature CAD‡
2. Adults with no pre-treatment LDL-C levels available but with a personal history of premature CAD‡ and family history of both hypercholesterolemia and premature CAD‡
3. Adults with persistent* LDL-C levels ≥160 mg/dl (without an apparent secondary cause of hypercholesterolemia†) in the setting of a family history of hypercholesterolemia and either a personal history or a family history of premature CAD‡

Evidence Grade: Class of Recommendation IIb, Strength of Evidence C-EO

Sturm, et al. JACC. V ol. 72 , N0 .6 , 2018

Recommendations for At-risk Relatives

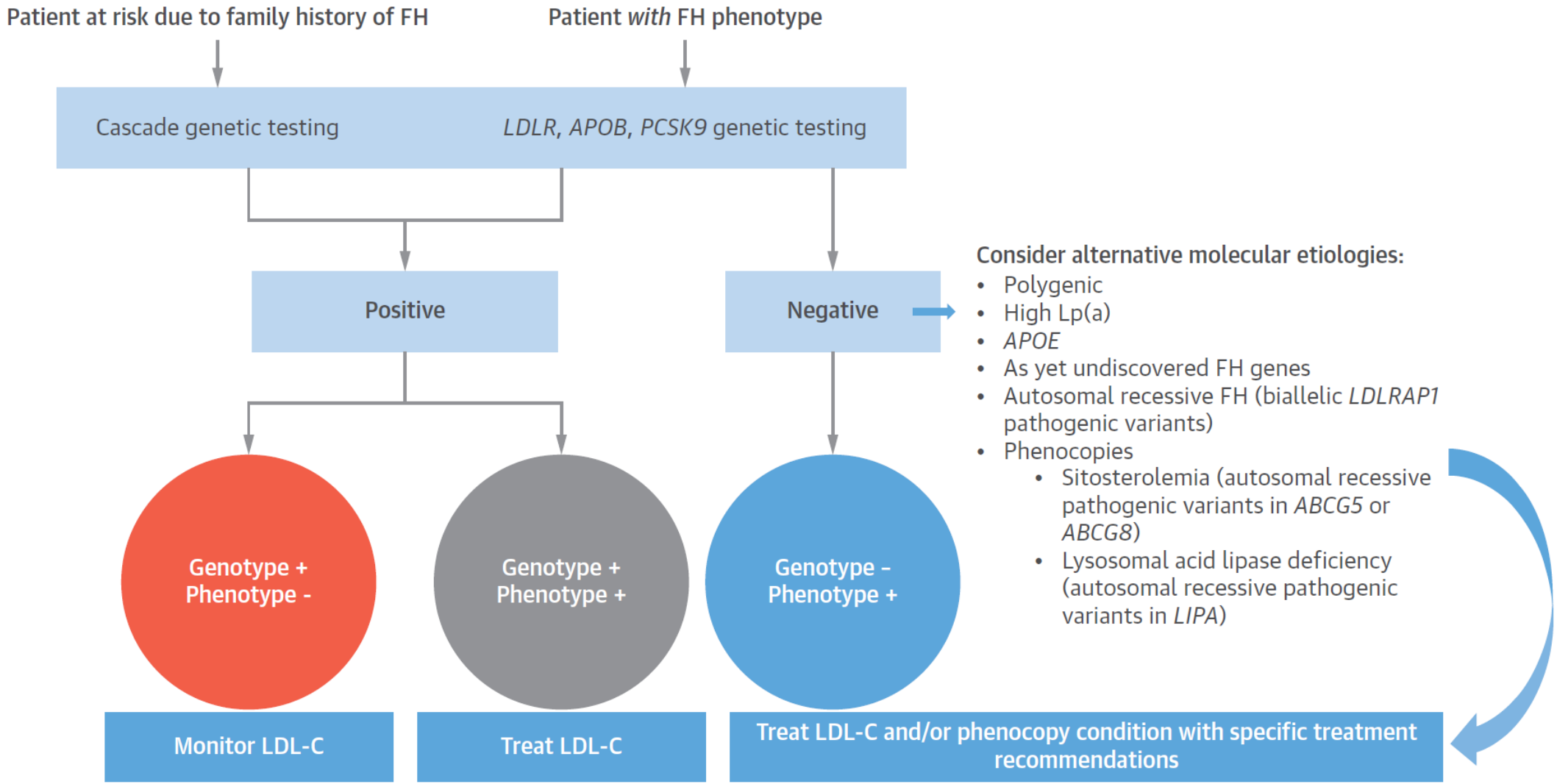
B. At-risk relatives

1. Cascade genetic testing for the specific variant(s) identified in the FH proband (known familial variant testing) should be offered to all first-degree relatives. If first-degree relatives are unavailable, or do not wish to undergo testing, known familial variant testing should be offered to second-degree relatives. Cascade genetic testing should commence throughout the entire extended family until all at-risk individuals have been tested and all known relatives with FH have been identified

Evidence Grade: Class of Recommendation I, Strength of Evidence B-R

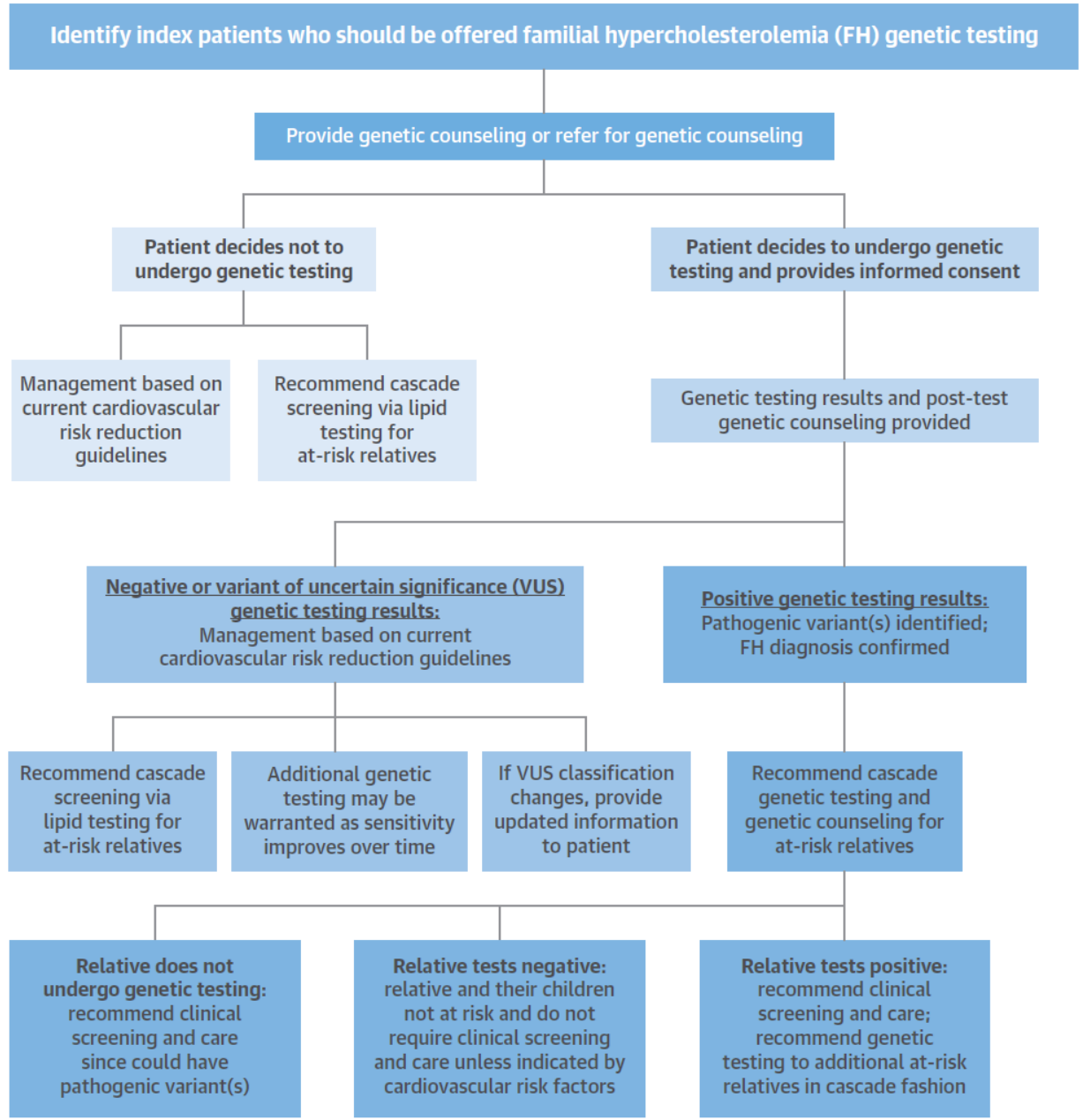
Sturm, et al. JACC. V ol. 72 , N0 .6 , 2018

FIGURE 2 **Different Categories of Patients May Undergo FH Genetic Testing**



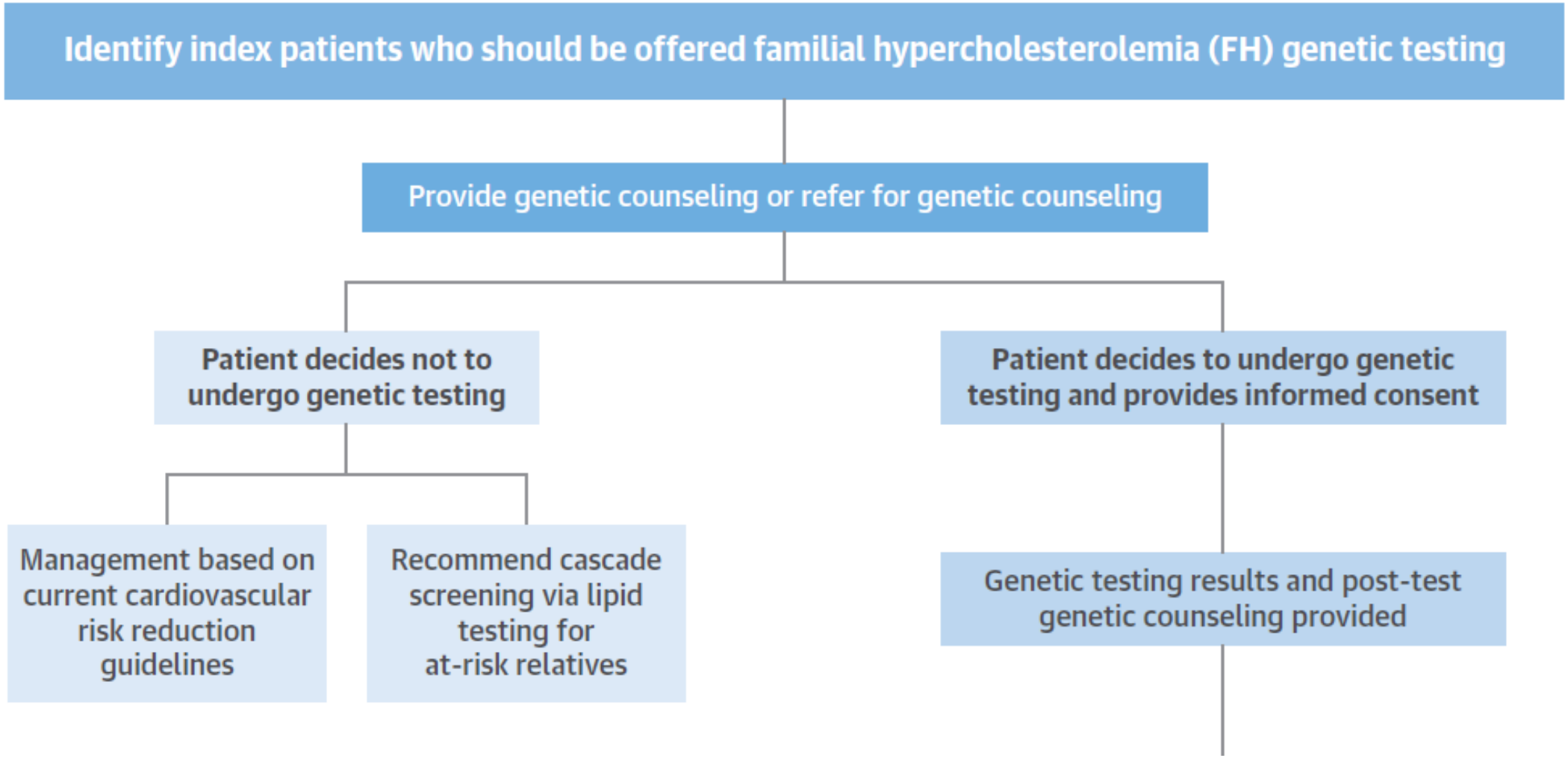
Individuals at risk due to family history as well as individuals with an FH phenotype may undergo FH genetic testing. The results of this testing can result in 3 categories of individuals: 1) genotype positive, phenotype negative; 2) genotype positive, phenotype positive; and 3) genotype negative, phenotype positive. In some cases, alternative molecular etiologies should be explored. Abbreviations as in **Figure 1**.

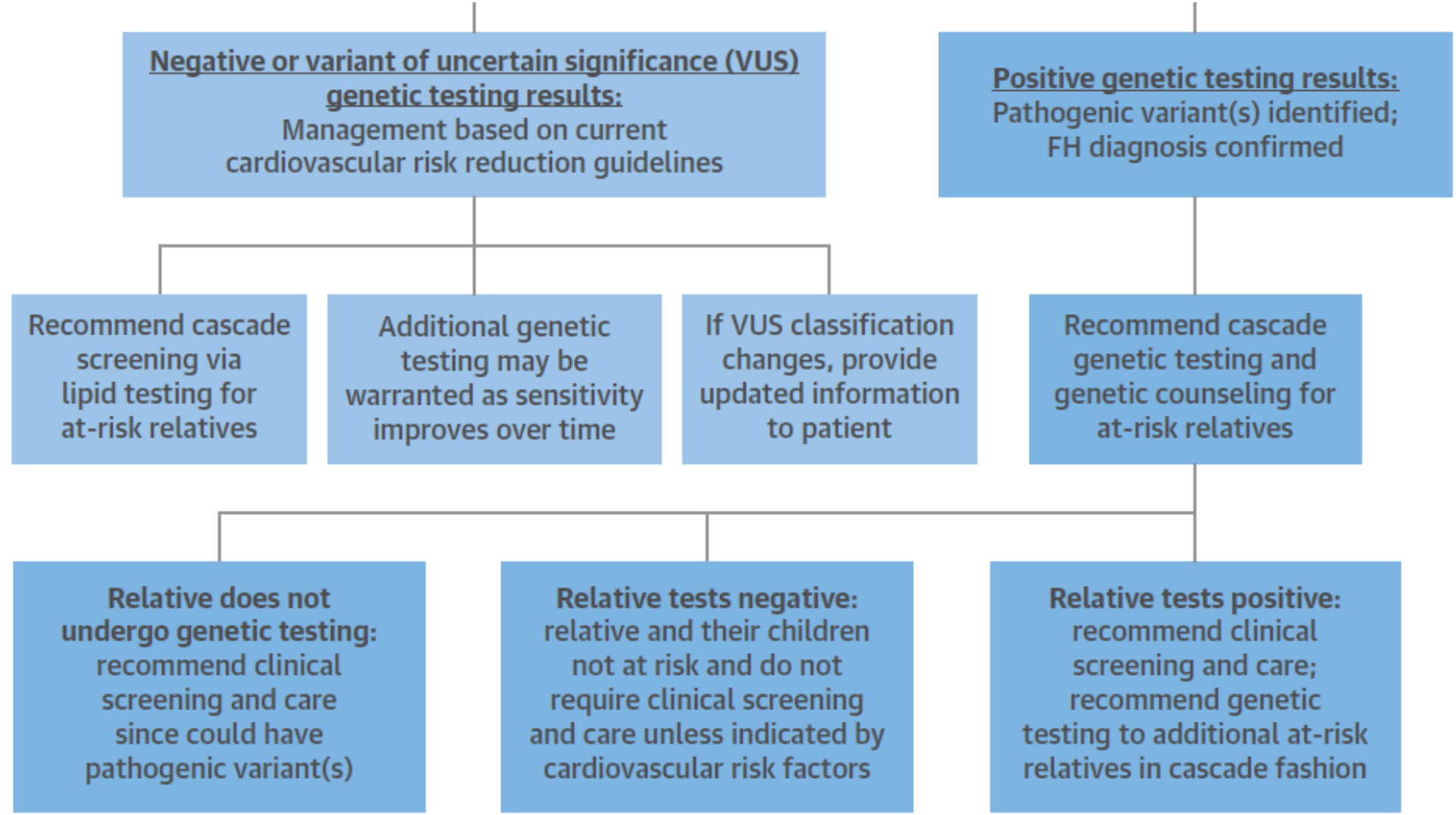
CENTRAL ILLUSTRATION The Genetic Testing Process in an Index Patient (Proband) and Family



Sturm, A.C. et al. J Am Coll Cardiol. 2018;72(6):662–80.

CENTRAL ILLUSTRATION The Genetic Testing Process in an Index Patient (Proband) and Family





Sturm, A.C. et al. J Am Coll Cardiol. 2018;72(6):662-80.

Genetic Testing Implications and Considerations

Benefits

- Confirms a definite dx
- Prognostic information
- Risk stratification
- Increase initiation and adherence to LLT with lower LDL
- Earlier tx
- Identification of potential “phenocopies"

Limitations

- Not completely sensitive or specific (VUS)

Potential Risks

- Genetic discrimination
- GINA
- Gaps in protection against disadvantaging individuals

Familial Implications

- Cascade testing
- Privacy
- Parental guilt
- Survival guilt

Cost

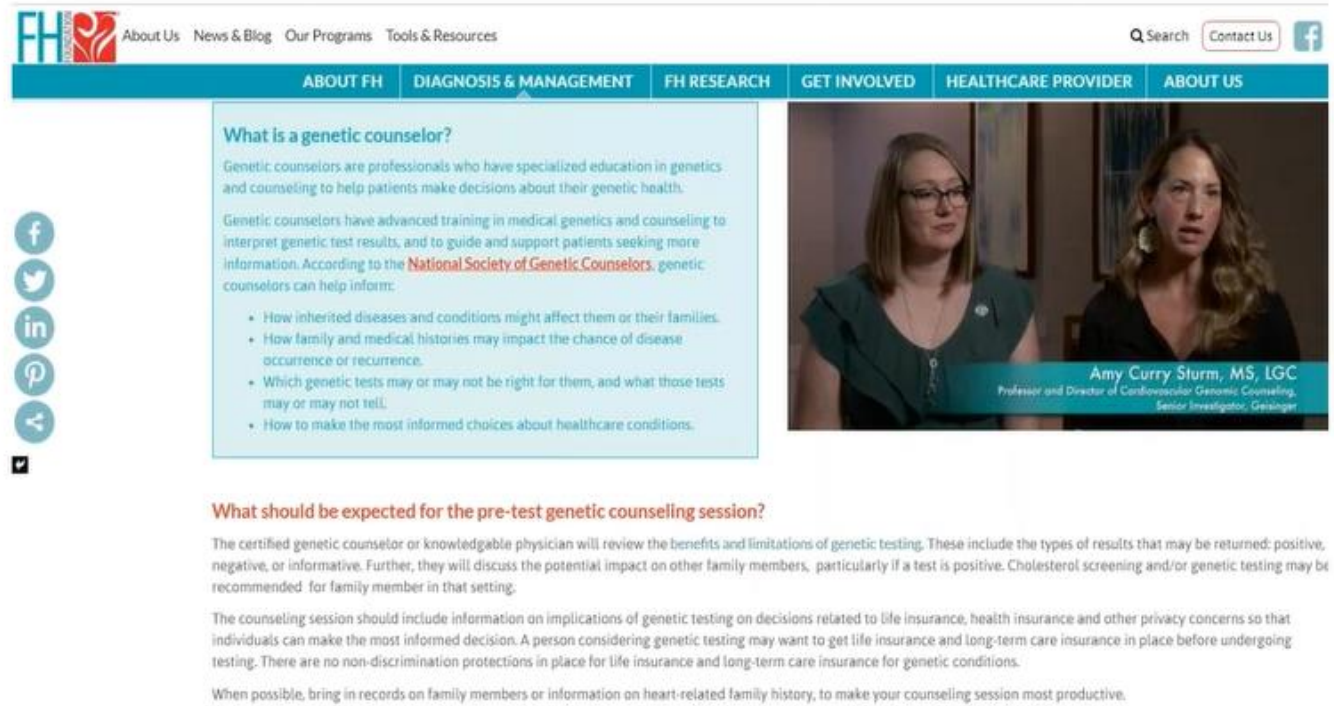
- $500-$1500
- Lack of insurance coverage

GINA GENETIC INFORMATION NONDISCRIMINATION ACT

Genetic Testing Resources Available via the FH Foundation

Table 3. The Genetic Counseling Process

- Pedigree collection
- Risk assessment
- Inheritance counseling
- Genetic testing facilitation
- Facilitation of family-based care and cascade testing
- Screening, prevention, and management options, in conjunction with physician
- Psychosocial counseling and anticipatory guidance
- Education and resources
- Research options



https://www.findageneticcounselor.com

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The Find a Genetic Counselor directory offers access to over 3,300 genetic counselors (US and Canada).

Check with your insurance company to verify coverage of genetic counseling, testing and authorized providers. For more information, visit AboutGeneticCounselors.com.

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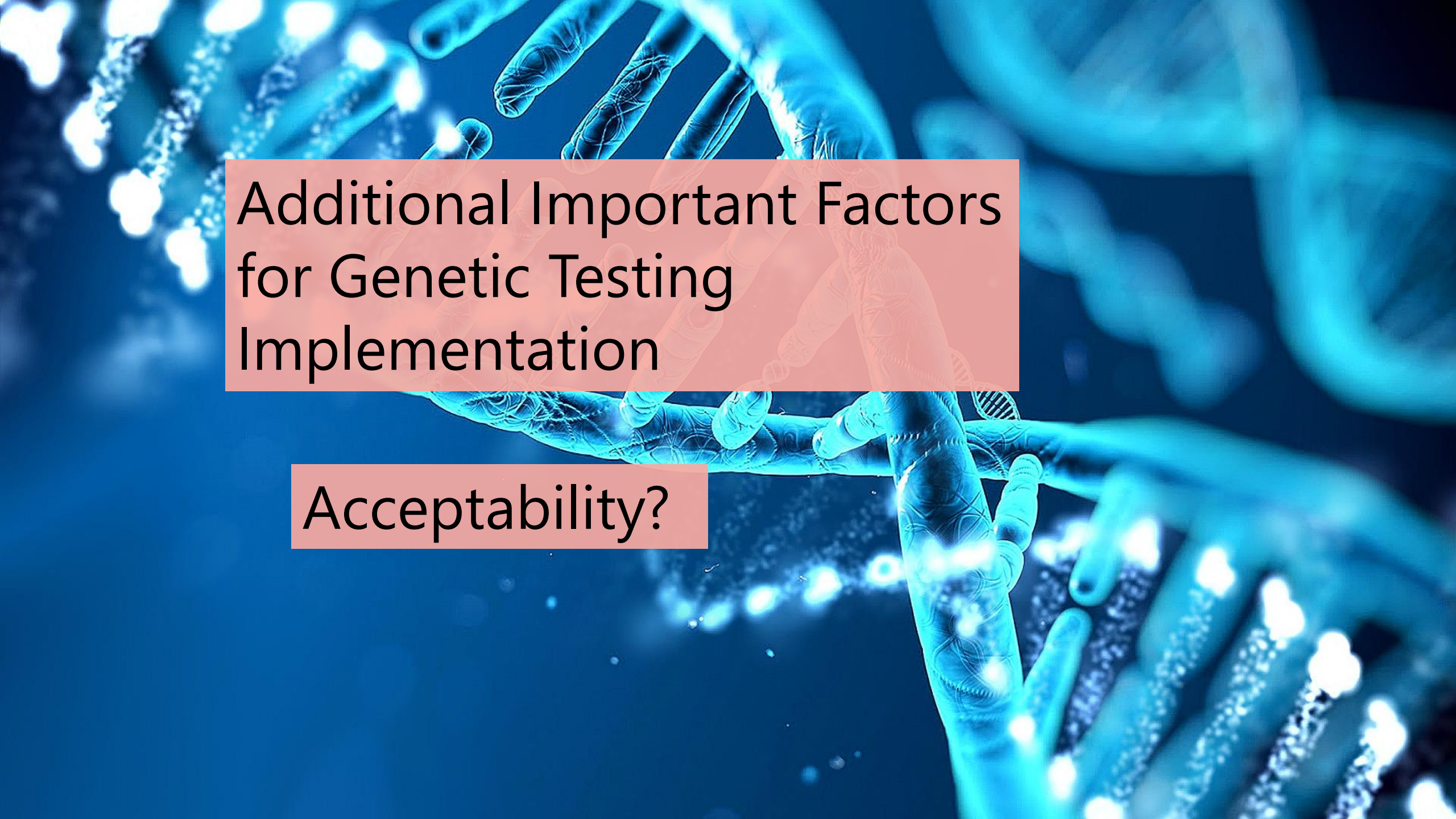
Additional searches:

- If you are a student, healthcare provider or other individual interested in speaking with a genetic counselor, click here.
- NSGC members are offered an expanded directory that contains additional information for use in searching for colleagues. Access the NSGC Member Directory.



Additional Important Factors for Genetic Testing Implementation

Acceptability?

Patient Education and Counseling 90 (2013) 372–377

Contents lists available at SciVerse ScienceDirect

Patient Education and Counseling

journal homepage: www.elsevier.com/locate/pateducou

Patient Perception, Preference and Participation

How do index patients participating in genetic screening programmes for familial hypercholesterolemia (FH) interpret their DNA results? A UK-based qualitative interview study

Nicholas Jenkins [a], Julia Lawton [a], Margaret Douglas [b], Simon Walker [c], Robert Finnie [d], Mary Porteous [e], Nina Hallowell [f,*]

- Non-threatening
- Receiving a positive result can be reassuring
  - Diet and lifestyle not primary cause of their condition
- For newly diagnosed patients, provide useful rationale for initiating LLT

J Community Genet
DOI 10.1007/s12687-016-0286-0

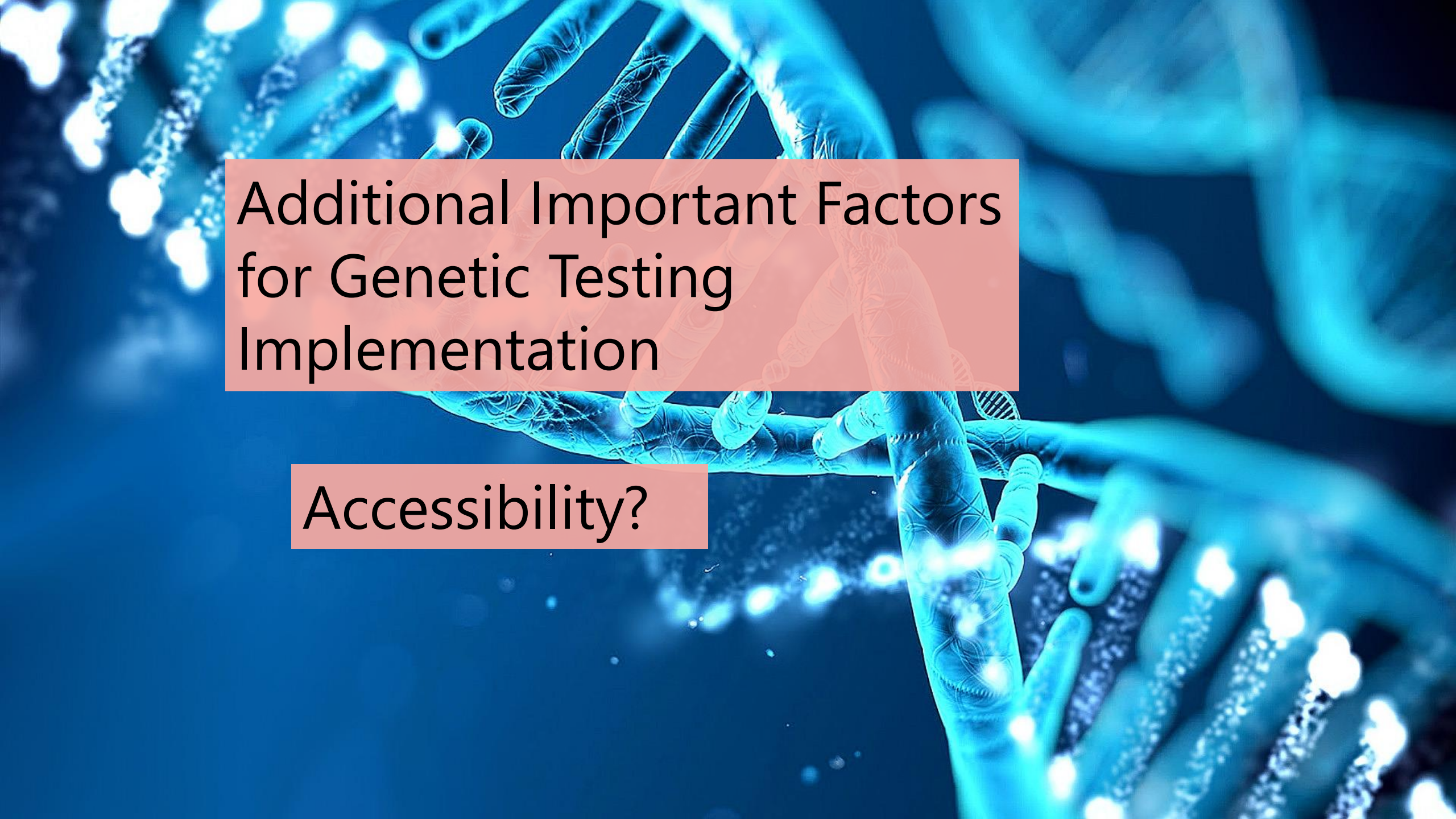
ORIGINAL ARTICLE

A qualitative study of patients' perceptions of the value of molecular diagnosis for familial hypercholesterolemia (FH)

Nina Hallowell[1] · Nicholas Jenkins[2] · Margaret Douglas[3] · Simon Walker[4] · Robert Finnie[5] · Mary Porteous[6] · Julia Lawton[7]

- Viewed DNA testing as an unexceptional event
- Viewed as a positive innovation because it confirmed their diagnosis
- Offered etiological explanation
- Provided information about theirs and family's risks
- Provides information for younger relatives to access genetic testing and thus, timely treatment

2016



Additional Important Factors for Genetic Testing Implementation

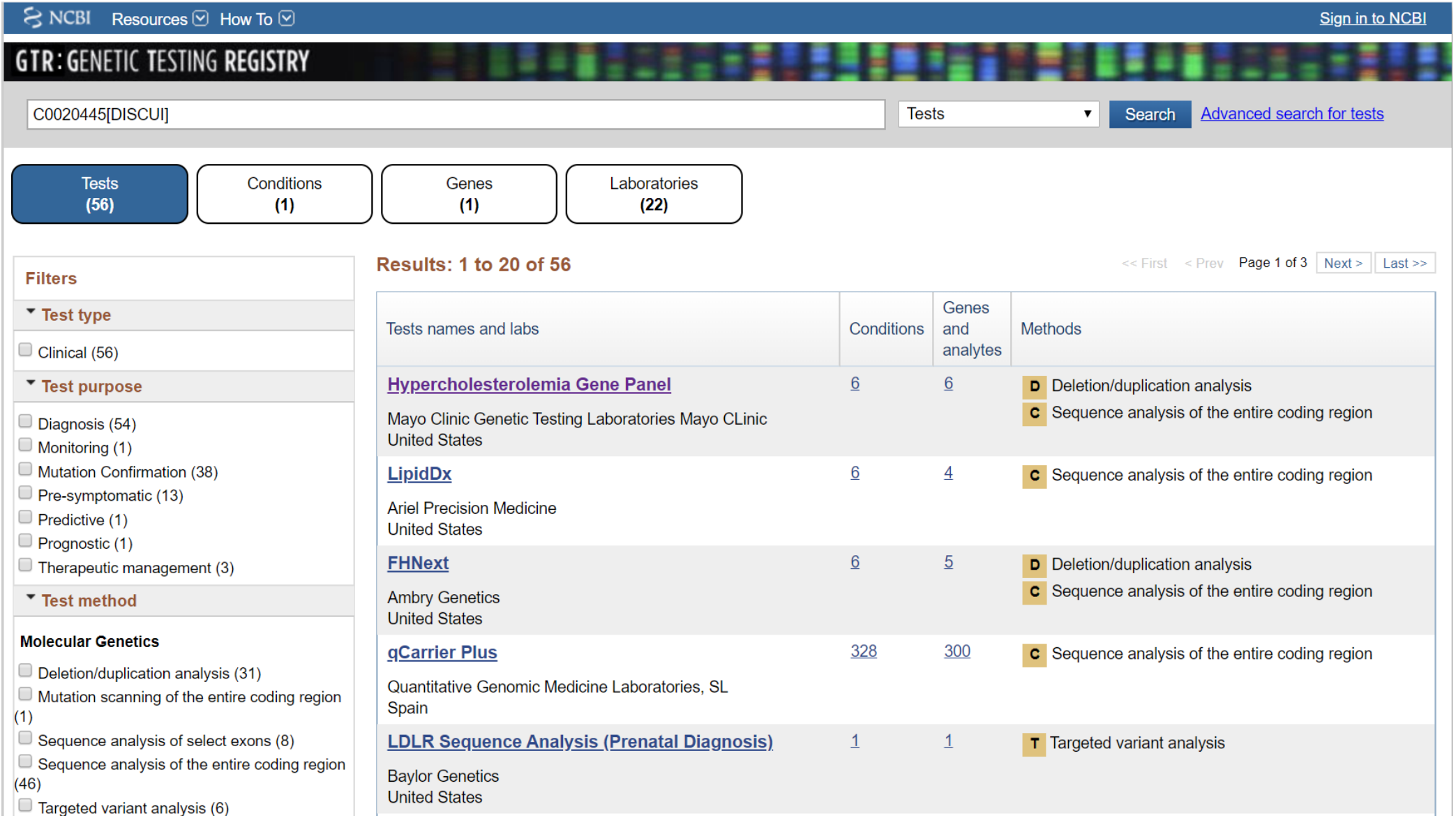
Accessibility?

Table 2. Targeted next-generation sequencing (NGS) panels commercially available for FH molecular diagnosis.

Service	Primary FH genes	Additional genes	CNV analysis	Turn-around time
FH Reflex Panel Mayo Clinic Rochester, MN, USA	*LDLR*, *APOB* (p.Arg3527)	None	*LDLR* Method: MLPA	2 weeks
FH NGS Panel DDC Clinic Middlefield, OH, USA	*LDLR, APOB, PCSK9*	*LDLRAP1*	None	4–6 weeks
FH Sequencing Panel Prevention Genetics Marshfield, WI, USA	*LDLR, APOB, PCSK9*	*LDLRAP1*	*LDLR, APOB, PCSK9* Method: aCGH	4 weeks
FH Panel GeneDX Gaithersburg, MD, USA	*LDLR, APOB, PCSK9*	*LDLRAP1*	*LDLR, APOB, PCSK9, LDLRAP1* Method: aCGH	4 weeks
FH Panel Invitae San Francisco, CA, USA	*LDLR, APOB, PCSK9*	*LDLRAP1*	*LDLR, APOB, PCSK9, LDLRAP1* Method: NGS data	1–3 weeks
FHNext Panel Ambry Genetics Aliso Viejo, CA, USA	*LDLR, APOB, PCSK9*	*LDLRAP1, SLCO1B1*(SNP c.521T>C)	*LDLR, APOB, PCSK9* Method: MLPA, aCGH	2–3 weeks
GeneSeq: CAD/FH Profile Integrated Genetics Westborough, MA, USA	*LDLR, APOB* (556bp of exon 26), *PCSK9*	*ABCA1, APOA2, APOC3, PON2* *SHOC2* (exon 2), *AKAP9* (exon 18)	None	6–8 weeks
FH Panel ApolloGen Irvine, CA, USA	*LDLR, APOB, PCSK9*	*ABCA1, ABCG1/5/8, APOA1, APOE* *APOC2/3/4, CETP, LCAT, LIPA, LIPC,* *LPA, LPL, MYLIP, NPC1*	None	4 weeks
SEQPRO LIPO IS Progenika Biopharma San Marcos, TX, USA Derio, Spain	*LDLR, APOB* (part of exons 26 and 29), *PCSK9*	*LDLRAP1, APOE* (part of exon 4), *STAP1*	*LDLR* Method: MLPA	4–6 weeks
Hypercholesterolemia Panel Sophia Genetics Saint-Sulpice, Switzerland	*LDLR, APOB, PCSK9*	*LDLRAP1, APOE*	*LDLR, APOB, PCSK9, LDLRAP1, APOE* Method: NGS data	2–3 weeks
FH/Comprehensive Panel HealthInCode A Coruña, Spain	*LDLR, APOB, PCSK9*	*LDLRAP1, APOE, SLCO1B1* Comprehensive option includes: *ABCG5/8, LIPA, LPA, NPC1L1, ABCB1,* *AMPD1, CH25H, COQ2, CPT2,* *CYP2D6, CYP3A/5,* *PPARA, PYGM, RYR1, SLC22A8*	*LDLR, APOB, PCSK9, LDLRAP1* *APOE, SLCO1B1* Method: aCGH	1–3 weeks

CNV: copy number variation; CAD: coronary artery disease; MLPA: multiplex ligation-dependent probe amplification; aCGH: array comparative genomic hybridization; NGS: next-generation sequencing.

Sanger re-sequencing is used for regions with inadequate diagnostic coverage and to confirm detected pathogenic variants.



https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=C0020445[DISCUI]. Last accessed Jan. 20, 2020.

Hypercholesterolemia Gene Panel

Clinical test for Familial hypercholesterolemia
Offered by Mayo Clinic Genetic Testing Laboratories

GTR Test ID : GTR000569011.1
Last updated: 2019-08-21
Test version history

Overview | How To Order | Indication | Methodology | Performance Characteristics | Interpretation | Laboratory Contact

Test order code : FHRGP

Test name

Hypercholesterolemia Gene Panel (FHRGP)

Purpose of the test

This is a clinical test intended for : Diagnosis, Therapeutic management, Risk Assessment, Recurrence

Condition

6 conditions tested. Click Indication tab for more information.

Familial hypercholesterolemia, lab preferred: Familial hypercholesterolemias
Familial hypercholesterolemia 1 (FHCL1), lab preferred: Familial hypercholesterolemia
Familial hypercholesterolemia 2 (FCHL2), lab preferred: Hypercholesterolemia, autosomal dominant, type B
Familial hypercholesterolemia 3 (FHCL3), lab preferred: Hypercholesterolemia, autosomal dominant, 3
Familial hypercholesterolemia 4 (FHCL4), lab preferred: Hypercholesterolemia, autosomal recessive
Sitosterolemia (STSL1) (STSL)

Methodology

Molecular Genetics

D Deletion/duplication analysis	Next-Generation (NGS)/Massively parallel sequencing (MPS) Illumina HiSeq 2500
C Sequence analysis of the entire coding region	Next-Generation (NGS)/Massively parallel sequencing (MPS) Illumina HiSeq 2500

Summary of what is tested

6 genes and variants. Click Methodology tab for more information.

Genes

Gene: ABCG5 (2p21)
Gene: ABCG8 (2p21)
Gene: APOB (2p24.1)
Gene: LDLR (19p13.2)
Gene: LDLRAP1 (1p36.11)
Gene: PCSK9 (1p32.3)

Conclusions

- FH Genetic testing provides a definitive diagnosis.
- Information from FH genetic testing provides prognostic and risk stratification data.
- FH genetic testing has personal utility.
- Cascade testing should be performed using DNA testing when the mutation is identified in the index patient.
- FH genetic testing is accepted and accessible.
- Genetic testing should be accompanied by genetic counseling.
- Patient and provider educational resources exist.