THE CHOLESTEROL DILEMMA

Clinical Features of Familial Hypercholesterolemia and Cascade Screening

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DISCLOSURE

NONE FOR THIS PRESENTATION

Presentation outline

1. Clinical features of Familial Hypercholesterolemia (FH)
2. Criteria for diagnosis of FH
3. Methods of Screening
4. Guideline Recommendations for Cascade Screening
5. Challenges of Cascade Screening
6. Call for screening children and young adults
7. Conclusion

Importance of History-Taking in Clinical Practice

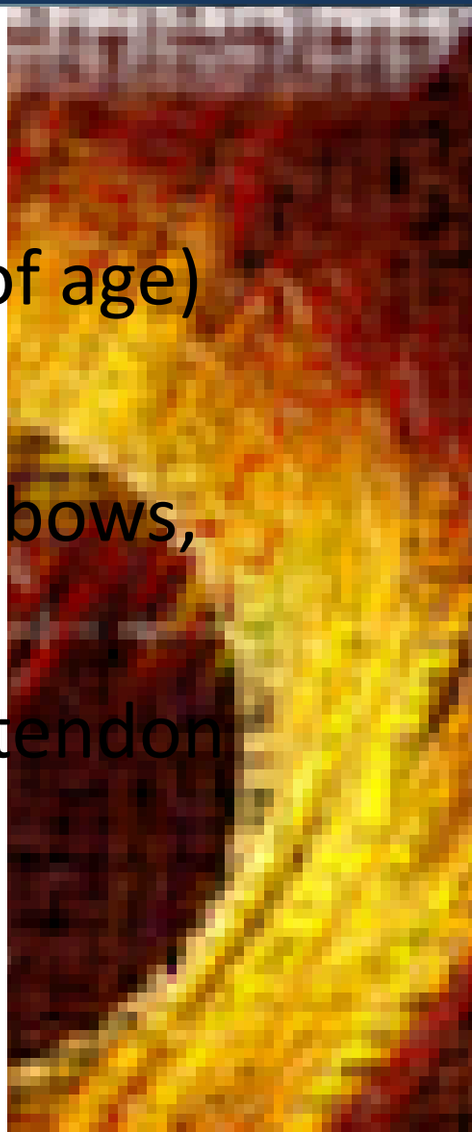
Check family history for premature cardiovascular disease (heart attack, stroke, peripheral vascular disease)

- Male first degree relatives, less than 55 years of age
- Female first degree relatives, less than 65 years of age

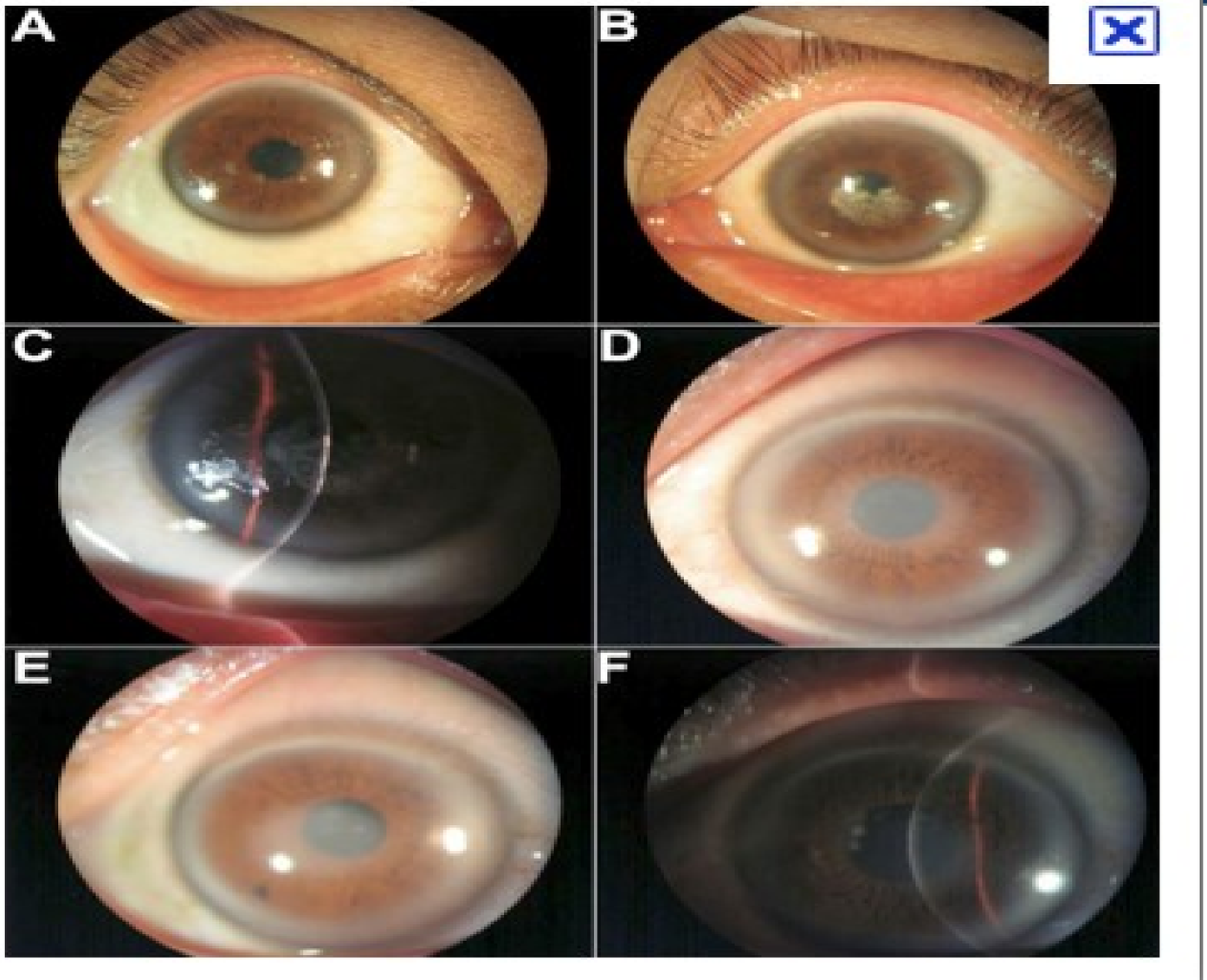
Phenotypic features of FH

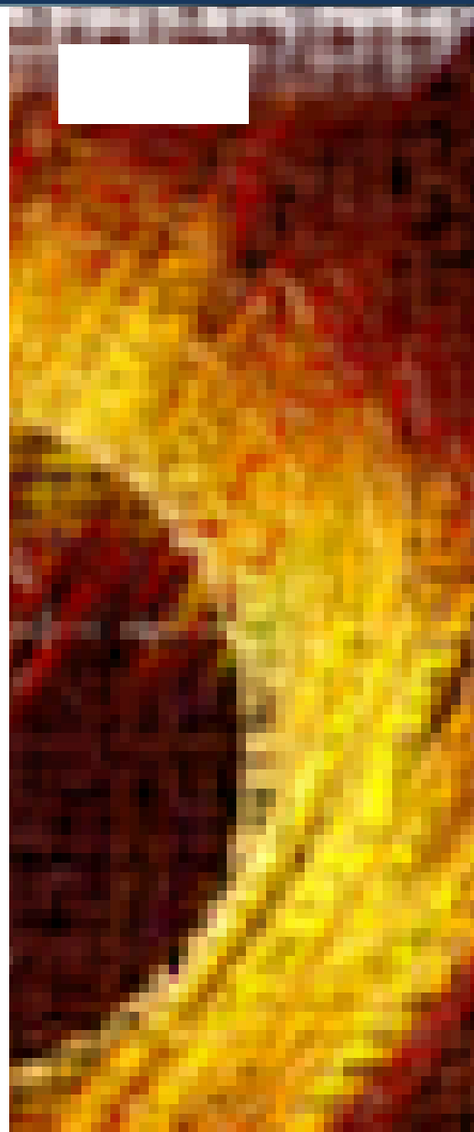
Phenotypic Features of FH

- Look for arcus cornealis in the eyes (less than 45 years of age)
- Watch out for xanthelasmas
- Look for cutaneous xanthomas at extensor surfaces – elbows, knees, finger joints
- Examine the Achilles tendon carefully – wide and thick tendon

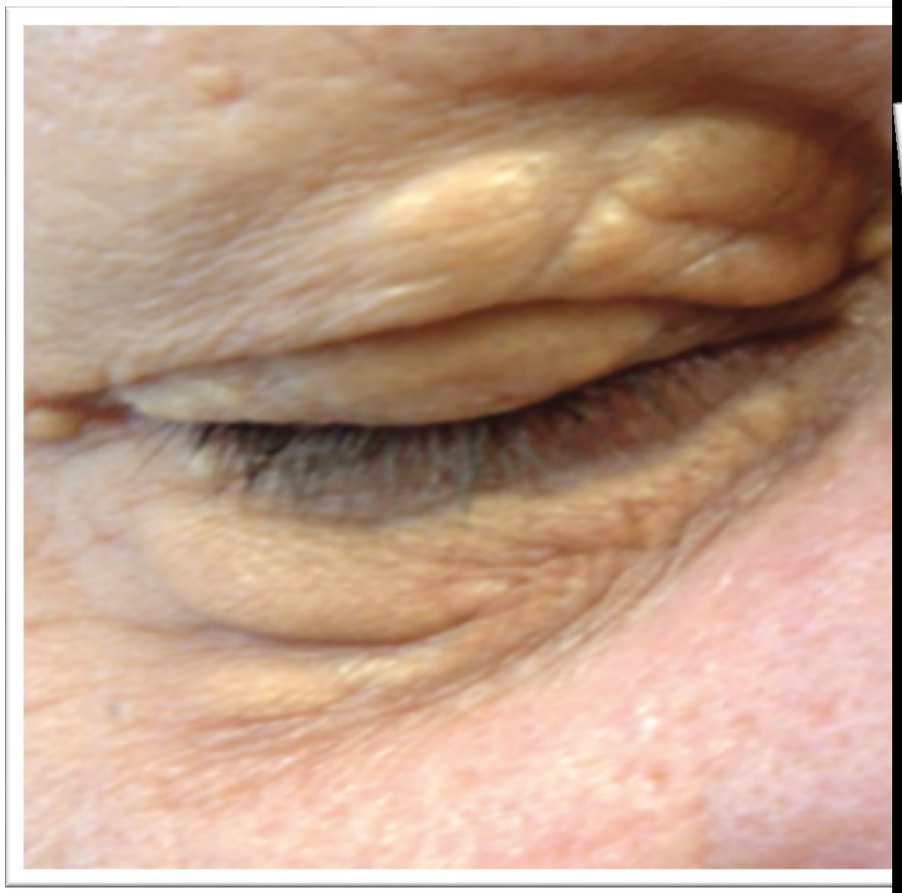


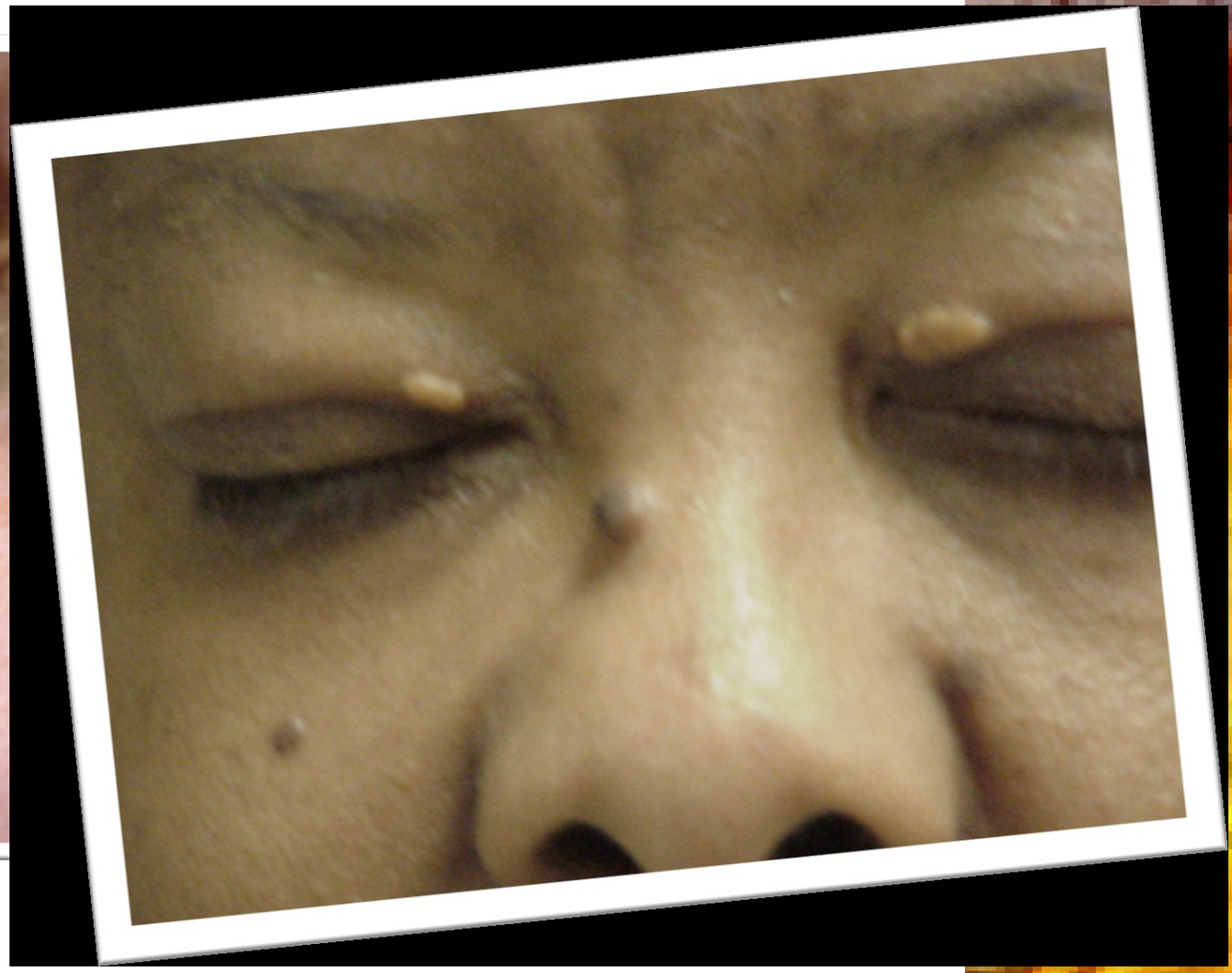
Physical Exam : Arcus cornealis



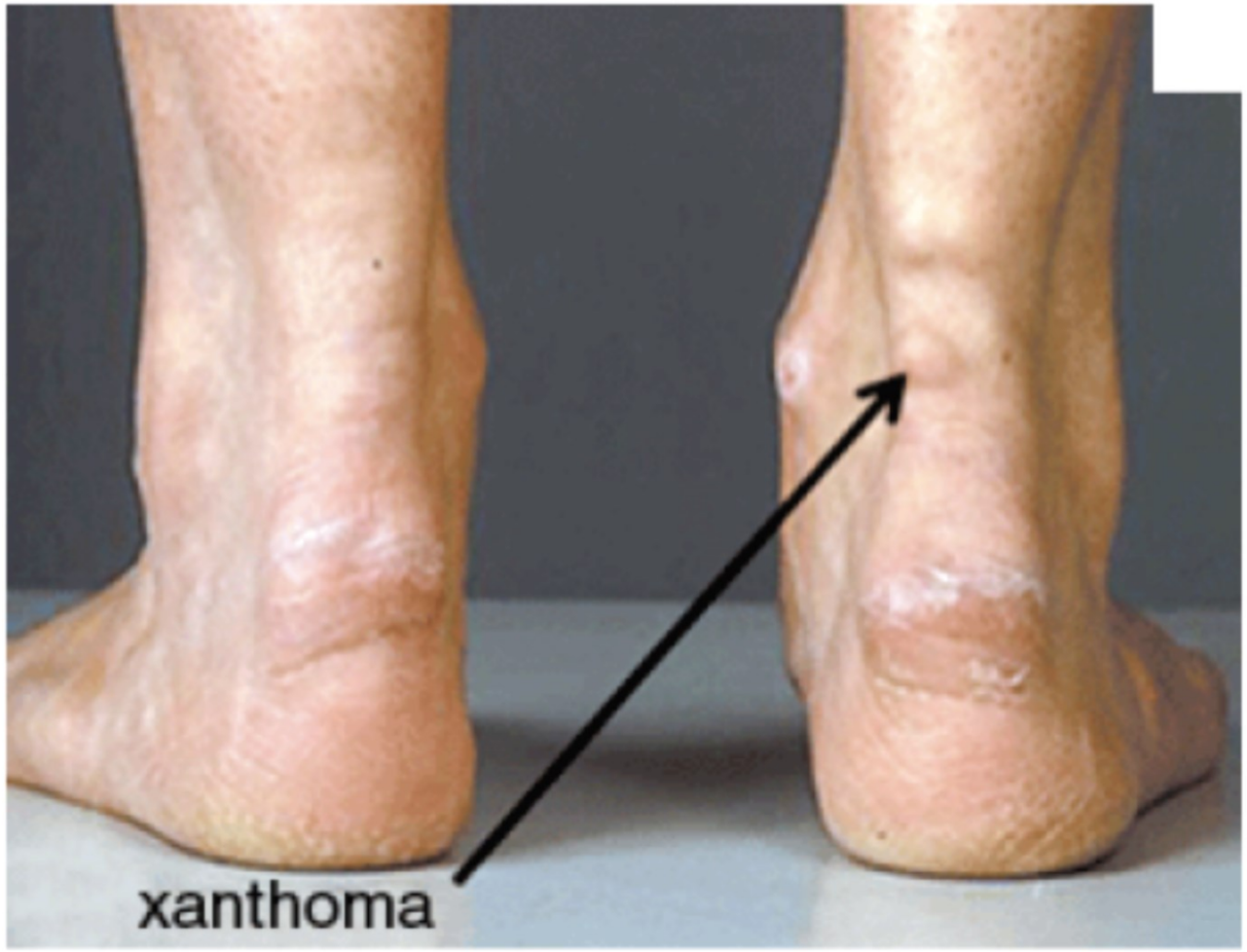


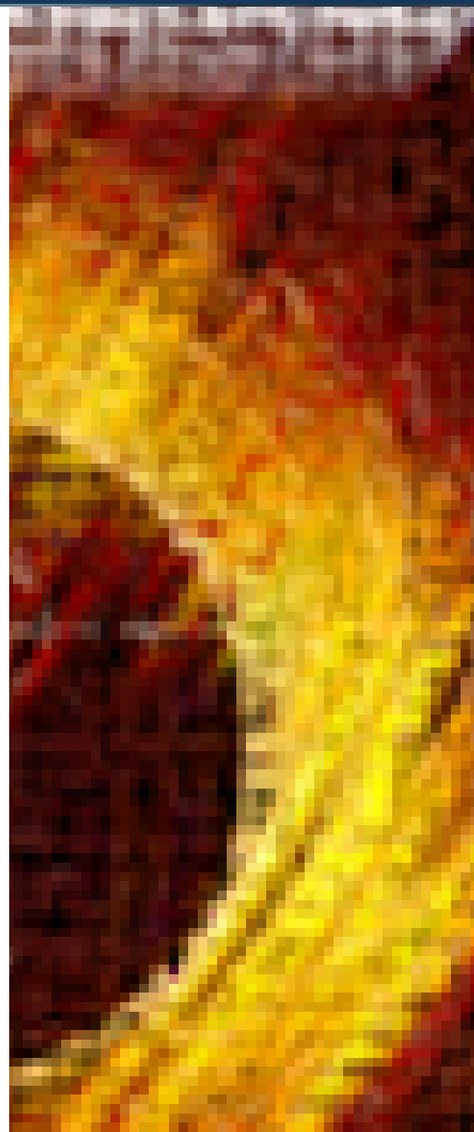
Physical Exam : Xanthelasma palpebarum



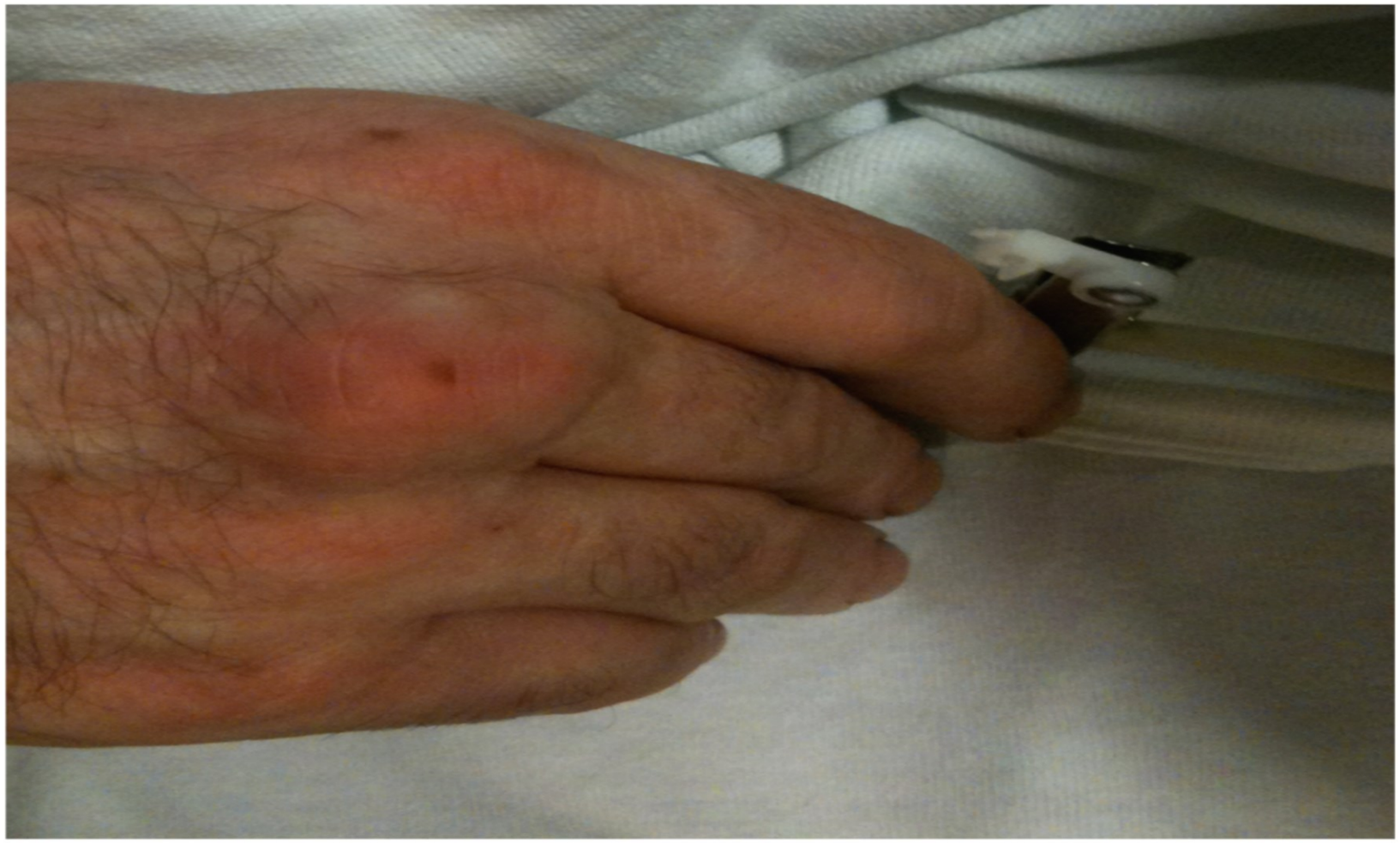


Physical Exam : Achilles Xanthomas

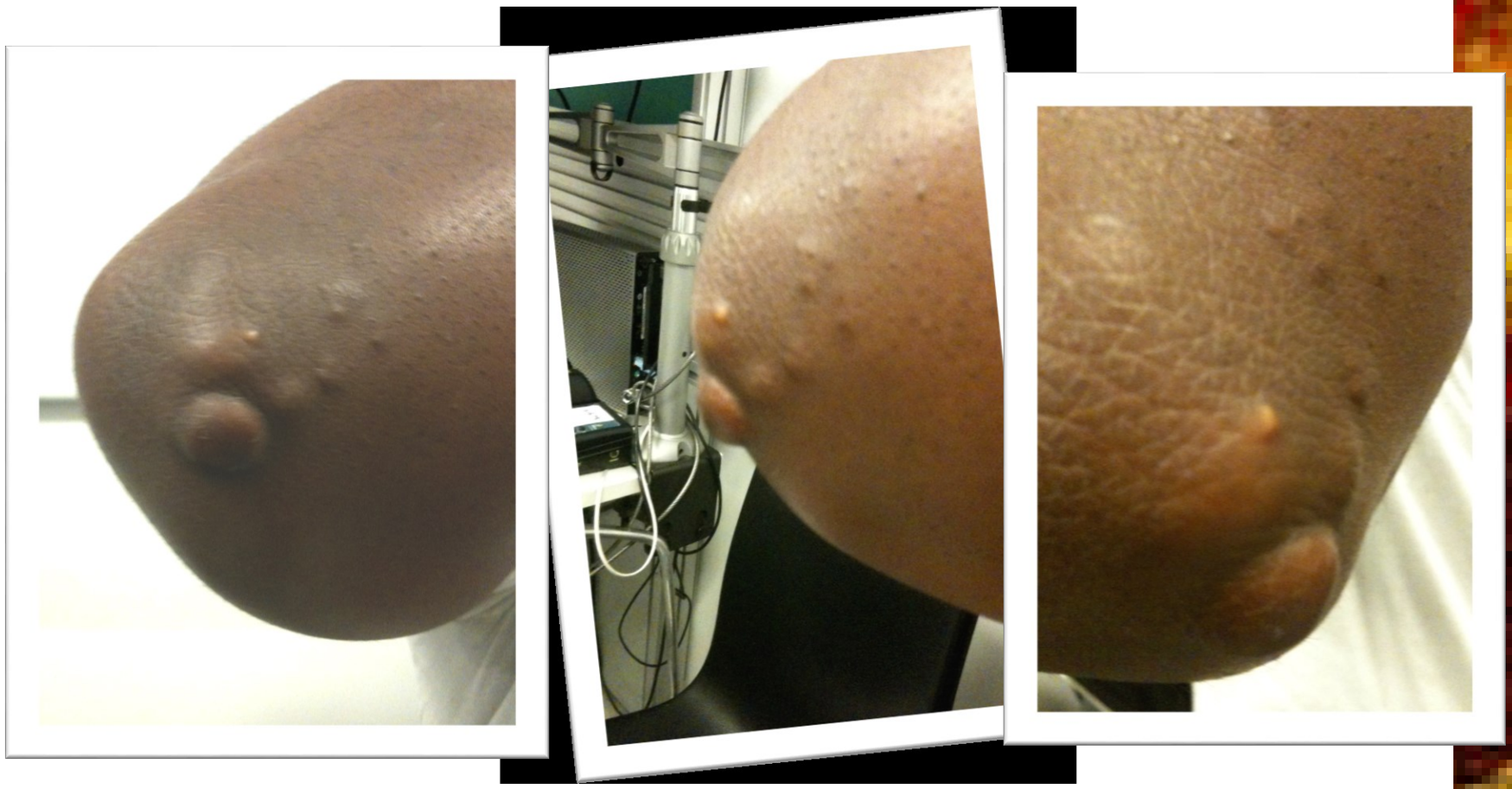




Physical Exam : Extensor Digit Xanthomas

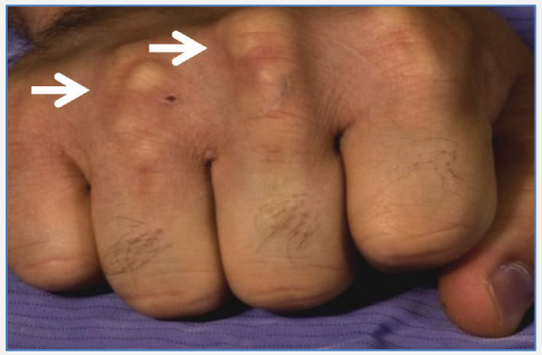


Physical Exam : Elbow Xanthomas



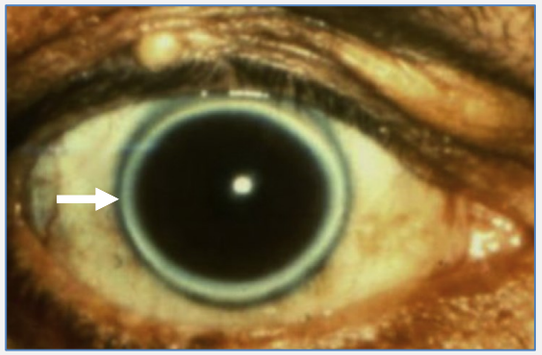
FH Phenotype Can be Characterized by LDL Deposition in Collagenous Connective Tissues[1]

Xanthomas[1,2]



- Tendon xanthomas may be present at any age and are most commonly found in the Achille tendon and finger extensor tendons, but can also occur in patellar and tricep tendons[3]
- In HoFH, cutaneous or tendon xanthomas may be present in children < 10 years old, and are highly suggestive of diagnosis[4]
- Variability in the age at appearance and extension of xanthomas can be partly explained by the underlying mutations; earlier appearance is associated with receptor-negative vs receptor-defective status[4]

Corneal Arcus[2]

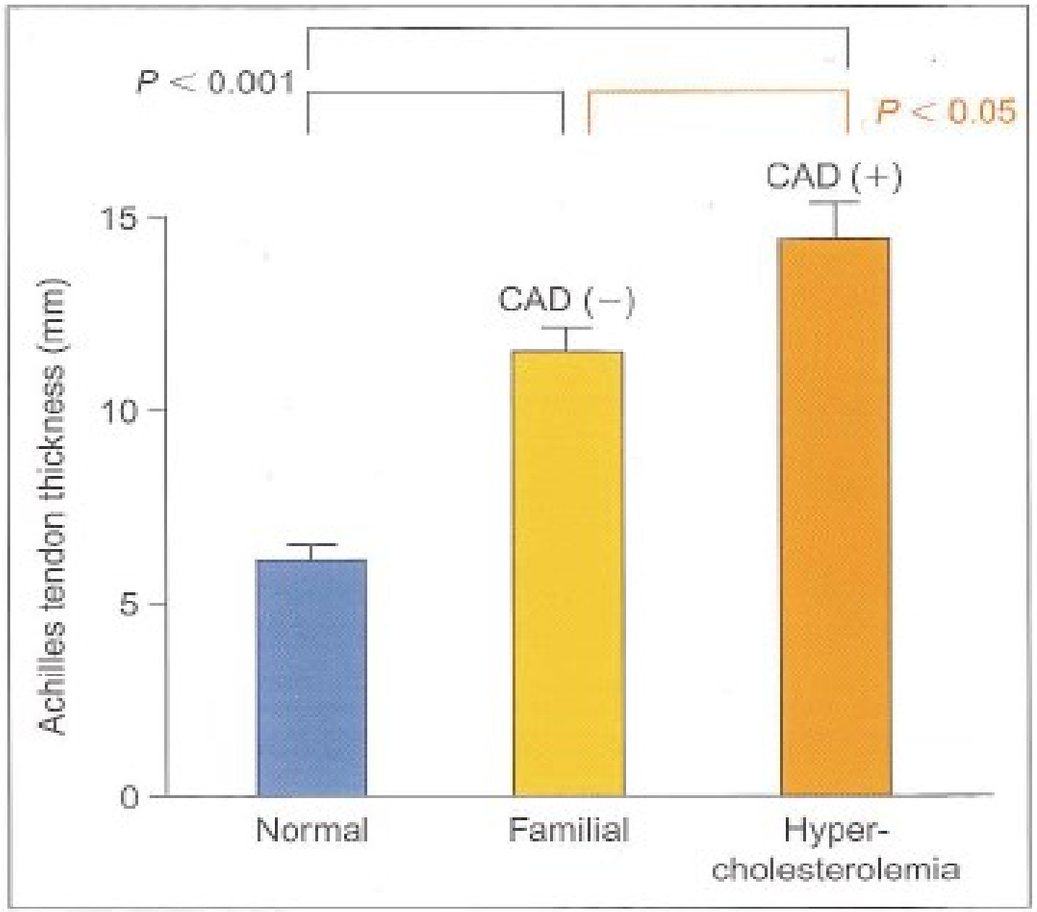


- The deposition of lipids in the human cornea, macroscopically observed as corneal arcus, is greatly accelerated in patients with HoFH[2]
- In addition to xanthomas, evidence of arcus corneae reinforces the clinical diagnosis of HoFH[4]

FH, familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; LDL, low-density lipoprotein.

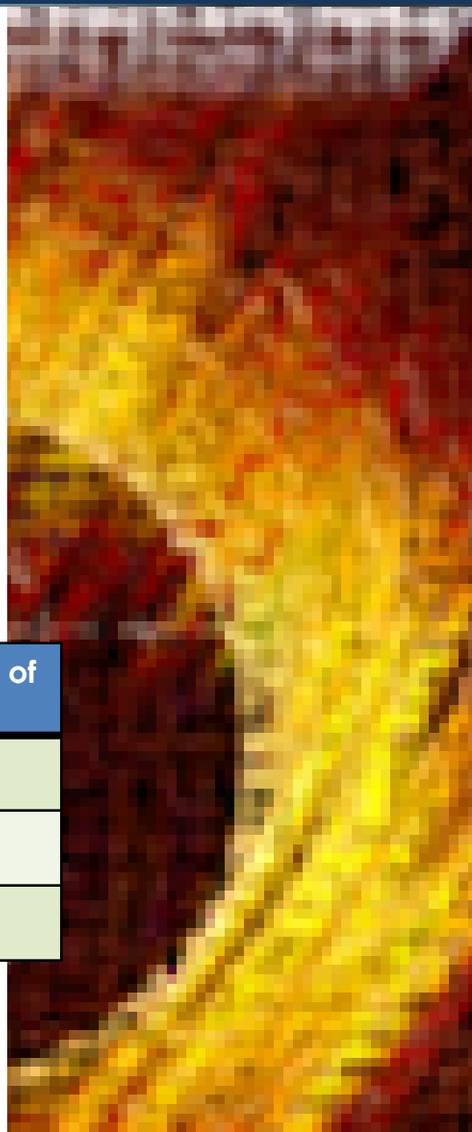
1. Zech LA, Hoeg JM. *Lipids in Health and Disease.* 2008;7(7). doi: 10.1186/1476-511X-7-7. 2. Genest J, et al. *Can J Cardiol*. 2014;30:1471-1481. 3. Goldberg AC, et al. *J Clin Lipidol.* 2011;5:S1-S8. 4. Cuchel M, et al. *Eur Heart J*. 2014;35:2146-2157.

Tendon Xanthoma Thickness in FH patients With or Without Coronary Artery Disease



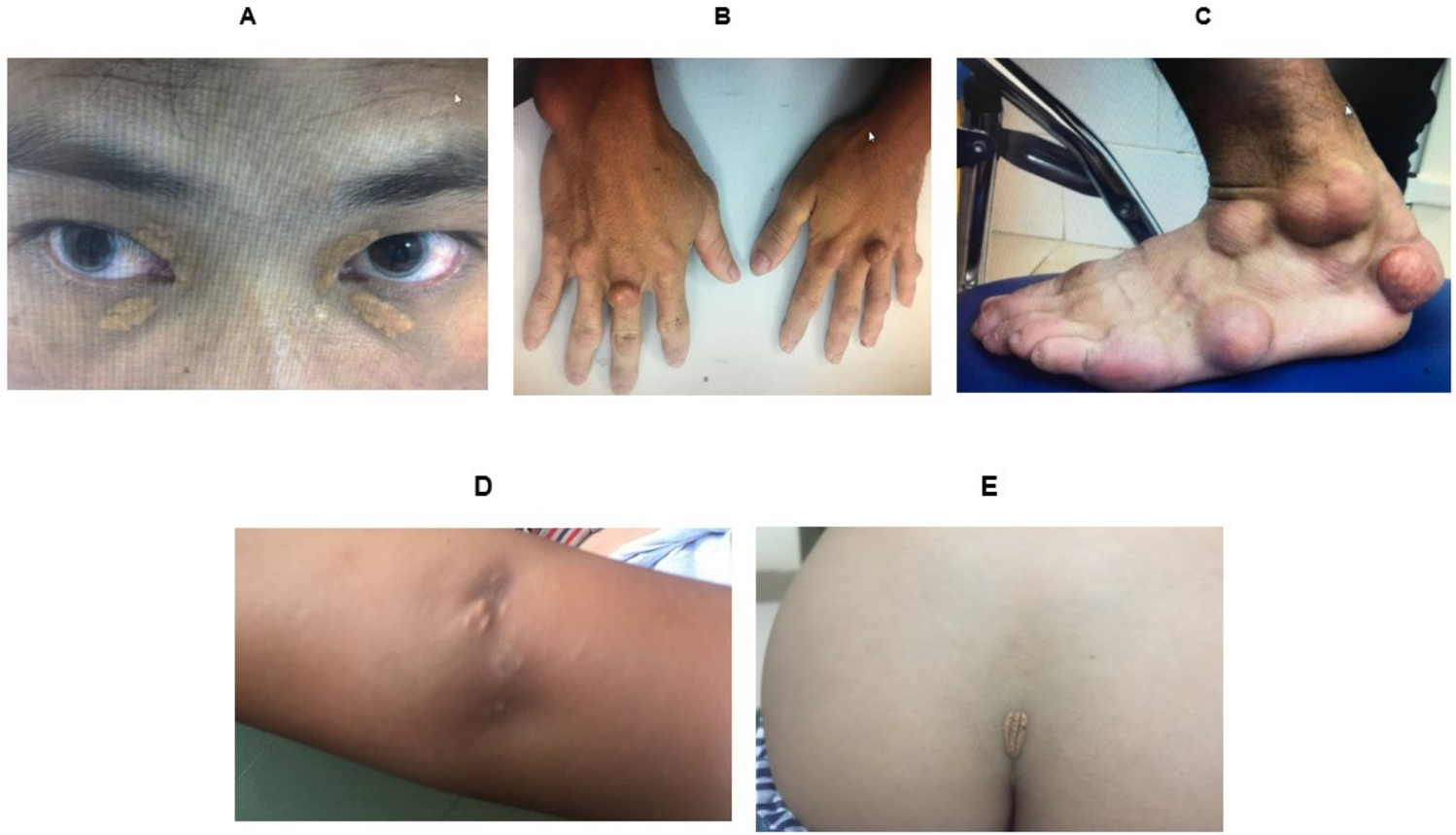
Severity of clinical manifestations is a function of the magnitude of the hypercholesterolemia, its duration and the presence of other risk factors

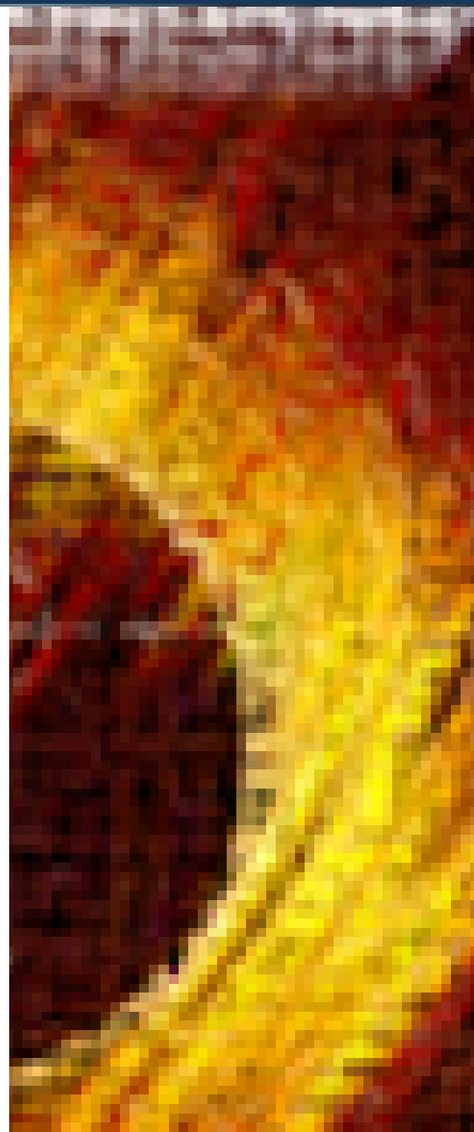
Subjects	Mean and SEM of Xanthomas
heterozygotes	12.5 ± 0.4 mm
homozygotes	18.6 ± 6.6 mm
normal	6.3 ± 0.2 mm



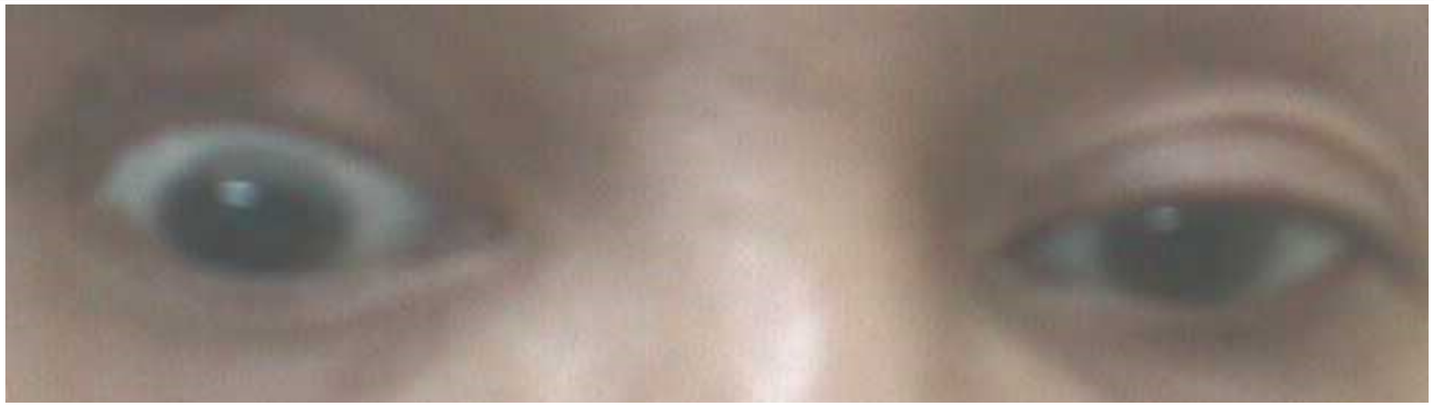
Mabuchi H et al., Achilles tendon thickness and ischemic heart disease in familial hypercholesterolemia. Metabolism, 27: 1672-1678

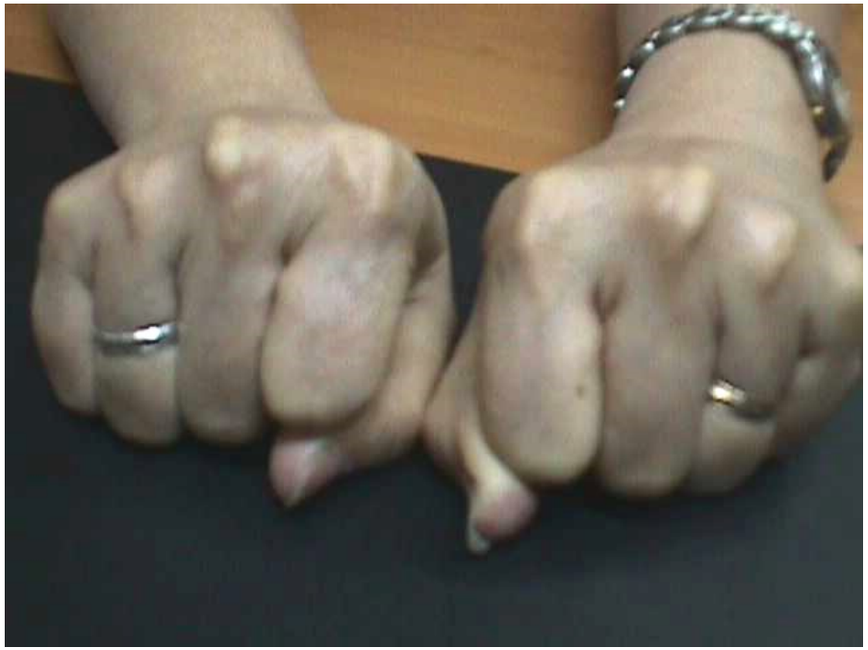
Findings in a HoFH Proband

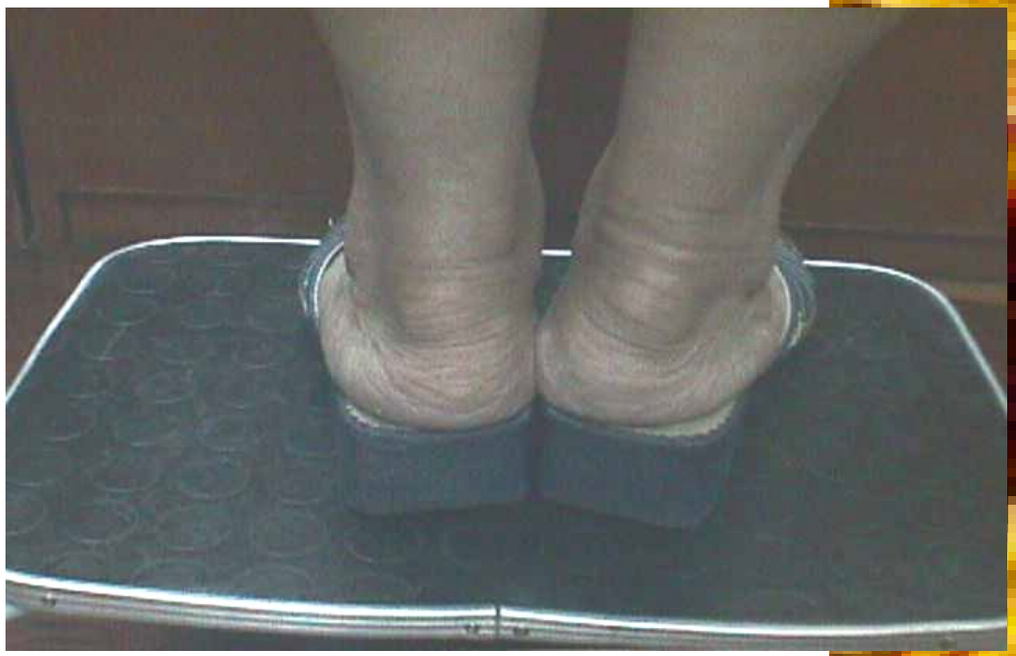




Heterozygous FH – Filipino patient, 40 year-old female







Criteria for the Diagnosis of FH

Multiple Screening Methods Are Available for FH

FH Diagnostic Resources		
Simon Broome Register Group (SBRG) – UK[1]	Definitive	TC > 290 mg/dL or LDL-C > 190 mg/dL + familial history of TX presence
	Possible	TC > 290 mg/dL or LDL-C > 190 mg/dL + familial history of MI or family history of hypercholesterolemia
Make Early Diagnosis to Prevent Early Death Program (MEDPED) – US[1]	Family with clinical suspicions of FH	Age < 20, TC > 270 mg/dL; Age 20–29, TC > 290 mg/dL; Age 30–39, TC > 340 mg/dL; Age ≥ 40, TC > 360 mg/dL
Dutch Lipid Clinic Network (DLCN) MEDPED[2,*]	Familial history	Hypercholesterolemia Premature vascular disease TX and/or corneal arcus Children aged < 18 with LDL-C > 95th percentile
	Personal clinical history	Premature (<55 years, men; <60 years, women) CHD, cerebral or peripheral vascular disease
	Physical exam	TX presence or corneal arcus (age < 45)
	LDL-C Levels	> 325 mg/dL; 251–325 mg/dL; 191–250 mg/dL; 155–190 mg/dL
	Molecular genetic testing	Causative mutation shown in the LDLR, APOB, or PCSK9 genes
Civeira et al. (Clinical criteria proposed for genetic testing)[1]	Familial history of TX + LDL-C ≥ 190 mg/dL	
	No family history of TX	Age < 30, LDL-C > 220 mg/dL Age 30–39, LDL-C > 225 mg/dL Age > 40, LDL-C > 235 mg/dL

*Scored for the diagnosis of FH: Definitive diagnosis > 8 points; Probable diagnosis 6-8 points.[2]
Note, only genetic testing can provide unequivocal FH diagnosis.[1]
FH, familial hypercholesterolemia; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; TC, total cholesterol; TX , tendon xanthomas.

1. De Castro-Oros I. *App Clin Genet*. 2010;3:53-64. 2. Nordestgaard BG, et al. *Eur Heart J*. 2013;34:3478-3490.

The Simon Broome Diagnostic Criteria Can Be Used to Establish a Clinical Diagnosis for FH

Criteria	Description
A	Total cholesterol levels > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (189 mg/dL) in adults Total cholesterol levels > 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (154 mg/dL) in children < 16 years of age
B	Tendinous xanthomata in the patient or a first-degree relative
C	DNA-based evidence of an *LDLR* or *APOB* mutation
D	Family history of myocardial infarction before age 50 years in a second-degree relative or before age 60 years in a first-degree relative
E	Family history of raised total cholesterol concentration > 7.5 mmol/L (290 mg/dL) in a first- or second-degree relative

A definite diagnosis of FH requires criteria A and B and/or C

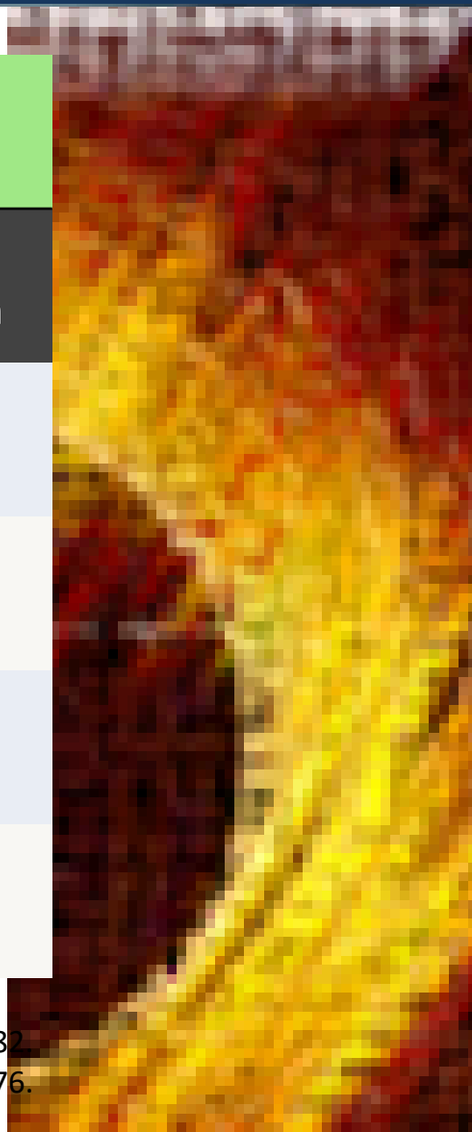
A probable diagnosis of FH requires criteria A and D and/or E

ApoB, apolipoprotein B; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; PCSK9, proprotein convertase subtilisin/kexin type 9.

Austin MA, et al. *Am J Epidemiol* 2004;160:407-420.

US MEDPED Program
Diagnostic Criteria for Probable Heterozygous FH

Age, years	Total cholesterol cut points, mmol/L (mg/dL)			
	1st degree relative with FH	2nd degree relative with FH	3rd degree relative with FH	General population
<20	5.7 (220)	5.9 (230)	6.2 (240)	**7 (270)**
20–29	6.2 (240)	6.5 (250)	6.7 (260)	**7.5 (290)**
30–39	7 (270)	7.2 (280)	7.5 (290)	**8.8 (340)**
>40	7.5 (290)	7.8 (300)	8 (310)	**9.3 (360)**



1. Singh S *et al*. *Curr Atheroscler Rep* 2015;17:482
2. Williams RR *et al*. *Am J Cardiol* 1993;72:171–176.

The DLCN Criteria Use a Scoring System To Establish a Clinical Diagnosis of FH

Category	Trait	Points
Family History	First-degree relative known with premature (men < 55 yrs, women < 60 yrs) CHD **OR** First-degree relative known with LDL-C > 95th percentile by age/gender for country	1
	First-degree relative with tendon xanthomata and/or arcus cornealis **OR** Children < 18 yrs with LDL-C > 95th percentile by age/gender for country	2
Clinical History	Premature (men < 55 yrs, women < 60 yrs) CHD	2
	Premature (men < 55 yrs, women < 60 yrs) cerebral or peripheral vascular disease	1
Physical Examination	Tendon xanthomas	6
	Corneal arcus in a person < 45 years	4
Biochemical Results (LDL-C)	> 8.5 mmol/L (> 325 mg/dL)	8
	6.5–8.4 mmol/L (251–325 mg/dL)	5
	5.0–6.4 mmol/L (191–250 mg/dL)	3
	4.0–4.9 mmol/L (155–190 mg/dL)	1
Genetic Testing	Causative mutation shown in the *LDLR*, *APOB*, or *PCSK9* genes	8

< 3 Unlikely FH | **3–5 Possible FH** | **6–8 Probable FH** | **> 8 Definite FH**

APOB, apolipoprotein B; CHD, coronary heart disease; DLCN, Dutch Lipid Clinic Network; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; PCSK9, proprotein convertase subtilisin/kexin type 9; yrs, years

Nordestgaard BG, et al. *Eur Heart J*. 2013;34:3478-3490.

Diagnostic criteria for FH (Adults) in Japan

1. LDL-cholesterol > 180 mg/dL (4.8 mmol/L)
2. Tendon or tuberous xanthomata
3. Close relative with FH or early CAD

Diagnosis

Definite FH: at least 2 of 3

Harada-Shiba et al J Atheroscler Thromb. 2012;19(12):1043-60.

China: FH Diagnostic Criteria

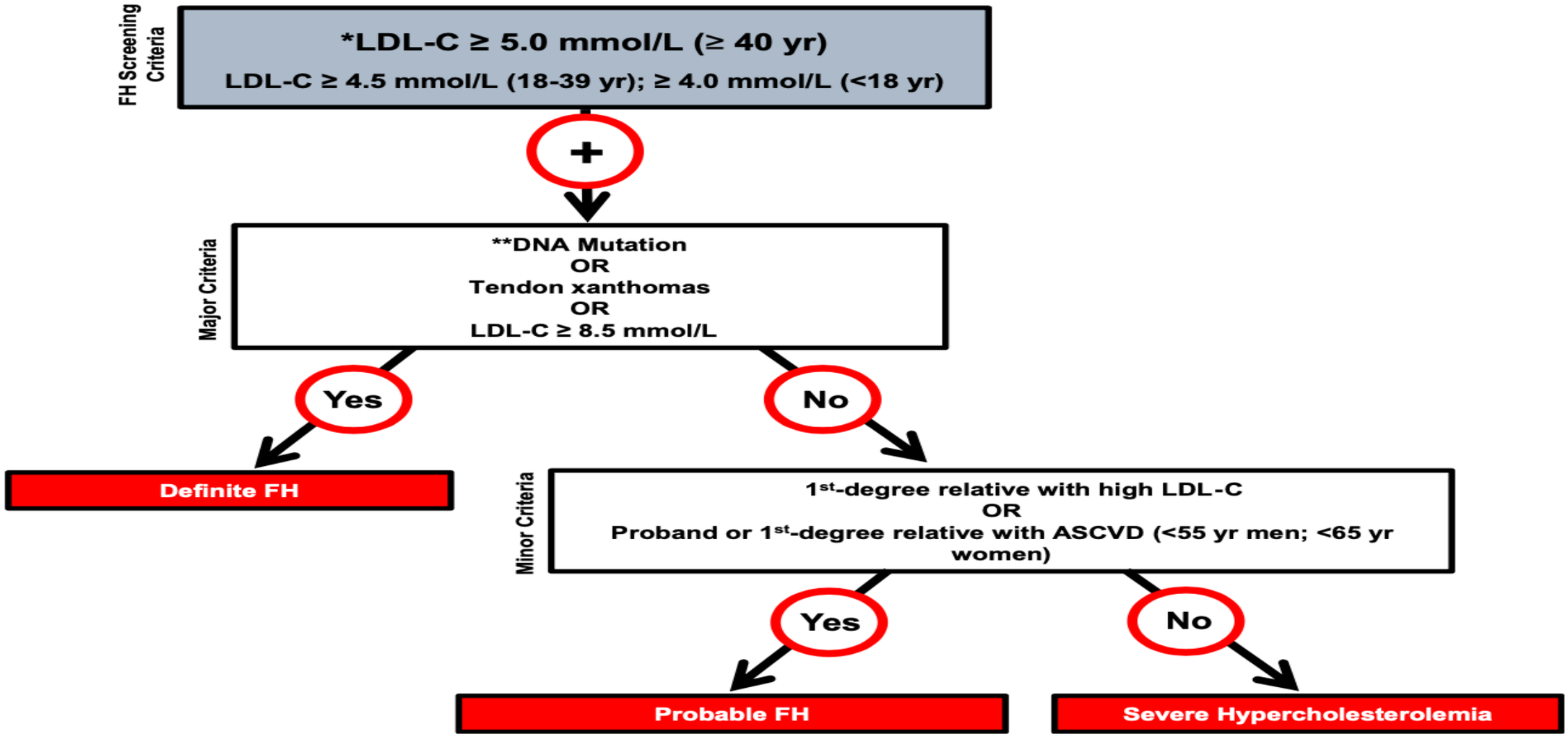
LDL-based Criteria

- LDLC ≥ 6 mmol/L or
- LDL-C ≥ 3.5 mmol/L plus a personal or family history of premature CHD

1. Zhou M *et al*. *J Atheroscler Thromb* 2016;23:539–549.
2. Shi Z *et al*. *Int J Cardiol* 2014;174:834–836.

Modified Dutch Lipid Clinic Network Criteria
Family history of a 1st degree relative with known premature CAD or vascular disease (1 pt)
Personal history of premature CAD (2 pts)
Premature cerebral vascular disease (1 pt)
LDL-C >6.0 mmol/L (8 pts); 5.0–5.9 mmol/L (5 pts); 3.5–4.9 mmol/L (3 pts); 2.5-3.4 mmol/L (1 pt)
Total score: >8 (definite), 6–8 (probable), 3–5 (possible), <3 (unlikely)

CANADA – Simplified FH Diagnosis



Ruel I, et. al. Can J Cardiol 2018; 34: 1210-2014.

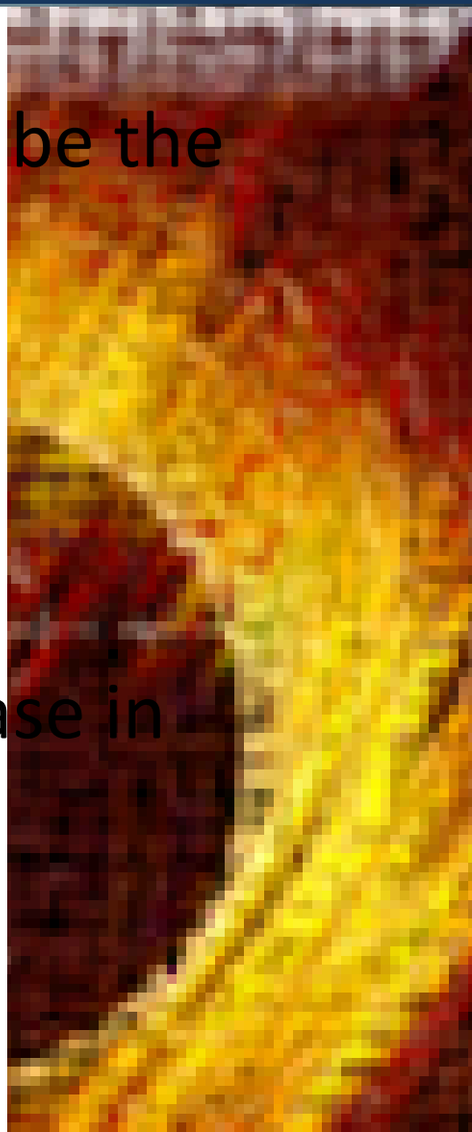
Forms of Screening to Identify Suspected FH Subjects

- Universal screening – general population
- Selective screening – special group or indication
- Cascade screening –work on proband
  - –Reverse cascade screening – child and parent

FH - An Important Health Problem

Many believe familial hypercholesterolemia (FH) should be the primary goal of cholesterol screening. Why FH?

1. Mortality rates from CHD in FH:
    a. 100x greater in those age 20-39
    b. 4x greater in those age 40-59
2. Children with untreated HeFH have a dramatic increase in risk of premature CHD after 20 years of age.



Youssef AA, Srinivasan SR, Elkasabany A, Chen W, Berenson GS. Trends of lipoprotein variables from childhood to adulthood in offspring of parents with coronary heart disease: the Bogalusa Heart Study. Metabolism. 2001; 50:1441–6.

Cascade Screening in the Diagnosis of FH

- As FH is dominantly inherited, cascade screening of family members can be highly effective at identifying other individuals with FH[1]
- Cascade screening relies on the initial identification of an FH patient, or proband[1]

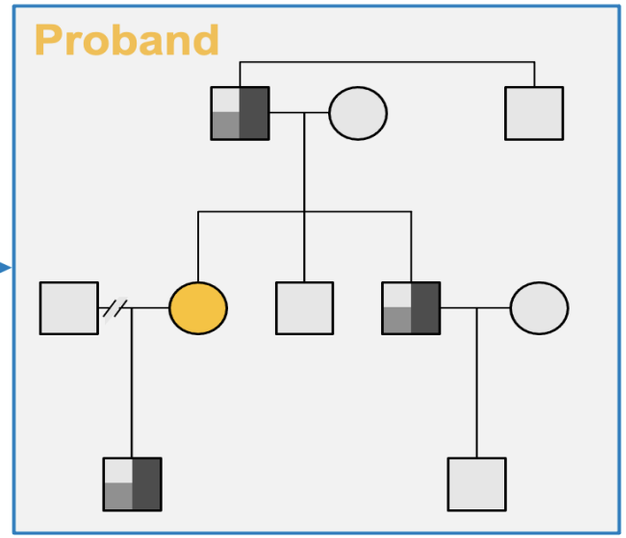
Adults[2]

- Plasma total cholesterol ≥ 310 mg/dL in an adult or adult family member(s) (or > 95th percentile by age and gender for country)
- Premature CHD in the subject or family member(s)
- Tendon xanthomas in the subject or family member(s)
- Sudden premature cardiac death in a family member

Children[2]

- Plasma total cholesterol ≥ 230 mg/dL in a child or child family member(s) (or > 95th percentile by age and gender for country)
- Premature CHD in the subject or family member(s)
- Tendon xanthomas in the subject or family member(s)
- Sudden premature cardiac death in a family member

FH diagnosis →

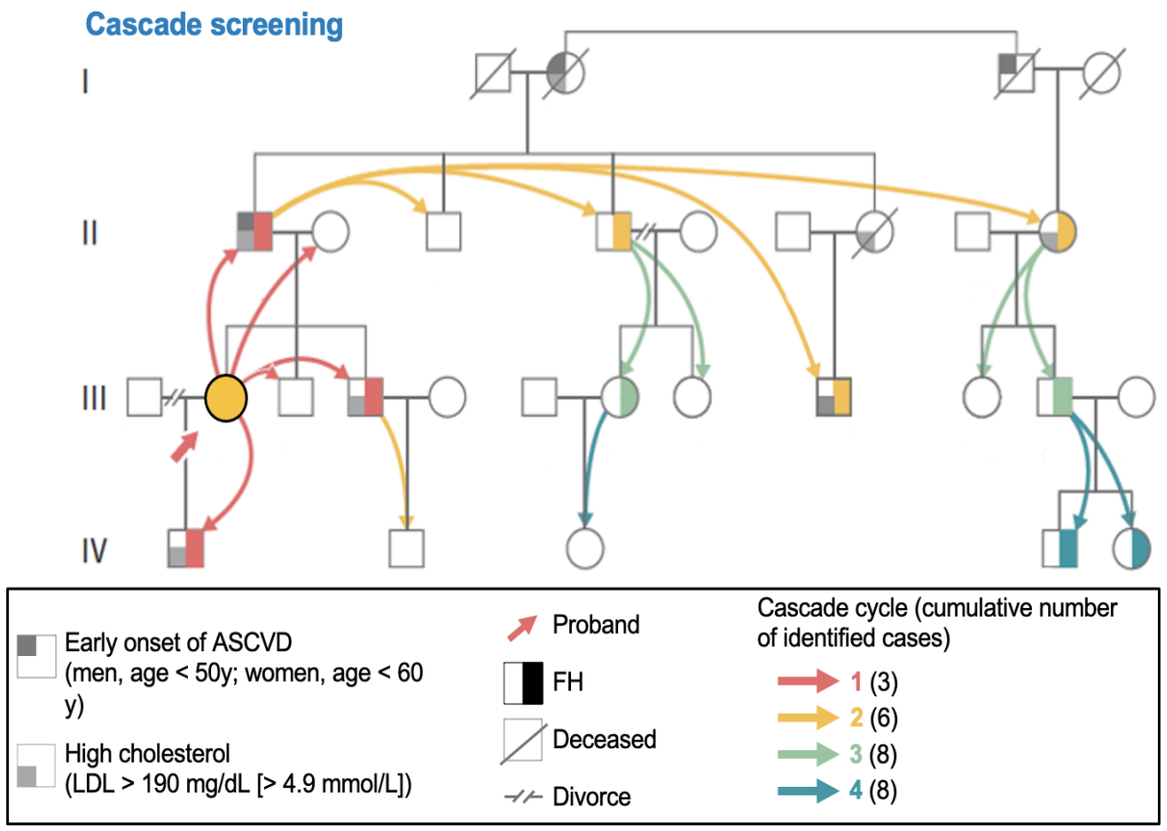


Cascade screening of the extended family of the known patient is an efficient method of identifying undiagnosed, affected individuals

1. Knowles JW, et al. *JAMA*. 2017;318(4):381-382. 2. Nordestgaard BG, et al. *Eur Heart J*. 2013;34:3478-3490.

Family-Based Cascade Screening To Identify Individuals with FH At-Risk for CV Events

- Once the patient has been identified, several steps of cascade screening are required to identify all patients with FH
- Screening cycles are repeated (cascaded) for each relative diagnosed with FH, thereby expanding the number of potential cases detected



Once an index patient with FH is identified, cascade screening starts with first-degree relatives (parents, siblings, children)

If the affected parent is identified, as many relatives as possible on that parent's side of the family should be screened

Children of the affected parent's siblings should also be screened because treatment in childhood is indicated for those who are affected

Each new FH case found via cascade screening then becomes a proband for broader cascading

Knowles JW, et al. *JAMA*. 2017;318(4):381-382.

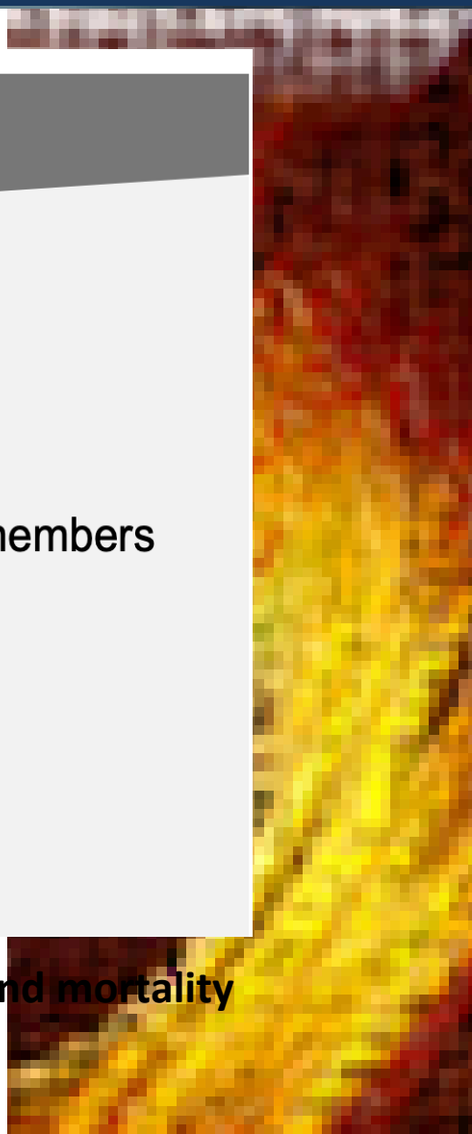
Advantages and Potential Barriers to Implementing Cascade Screening

Advantages

- More cost effective than other screening strategies
- Reduces average age of FH diagnosis
- Increases percentage of patients receiving LLT
  - In the Netherlands, on average 8 relatives with FH were identified per index case, significantly increasing the proportion of FH patients receiving treatment
- Improves treatment initiation and adherence

Potential Barriers

- Difficulties recruiting index cases
- Family structure and dynamics
- Geographic dispersion of family members
- Healthcare literacy
- Access to care
- Privacy concerns



Cascade screening for FH is an evidence-based intervention that can reduce the burden of morbidity and mortality from ASCVD and has been recommended by national and international organizations

Knowles JW, et al. *JAMA*. 2017;318(4):381-382.

Reverse Cascade Screening Can Be Used To Diagnose Individuals with FH

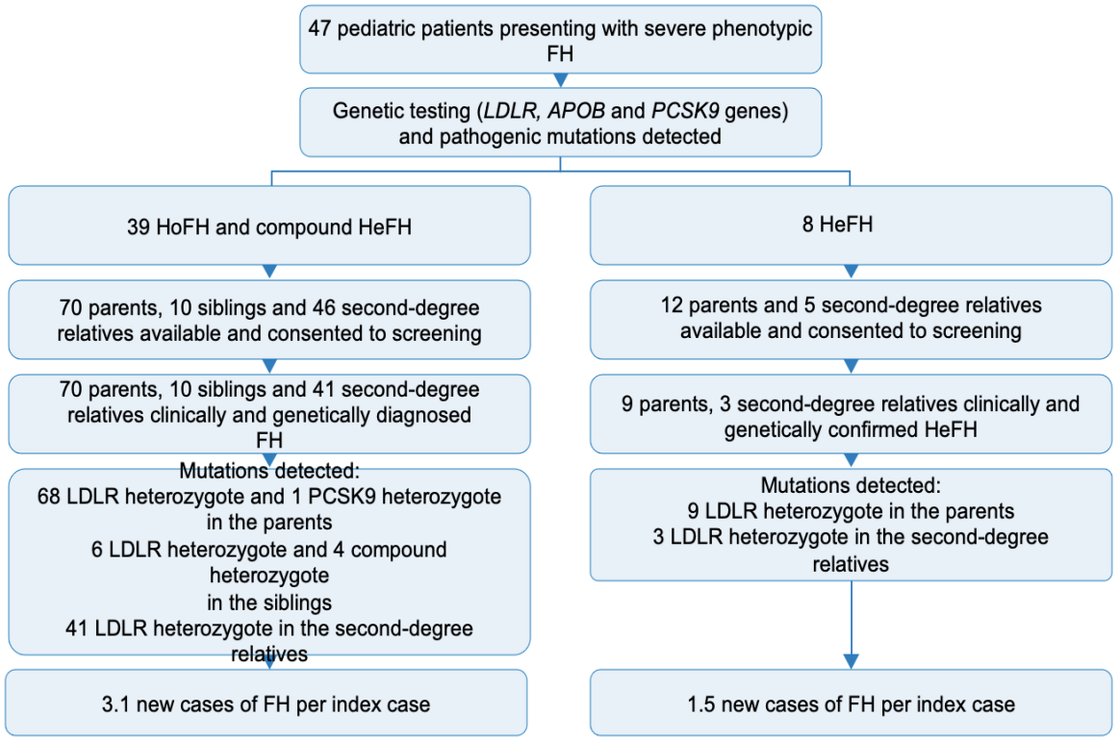
- Reverse cascade screening (or child-parent screening) can be used to identify most families with FH in a population[1]
- The LDL-C levels of children are tested when routine immunizations are provided (normally at age 1–2 years)[1]
- If a child tests 'positive' (> 1.5 times the median LDL-C levels of age-specific population) the parents are tested, with the parent with the higher LDL-C levels having a 96% probability of being correctly identified as the parent affected [2]

Reverse cascade screening was used to identify FH in families in China[3]

Children with HeFH or HoFH were identified and family members subsequently tested[3]

All first-degree family members screened had the same mutations as the 'index' child[3]

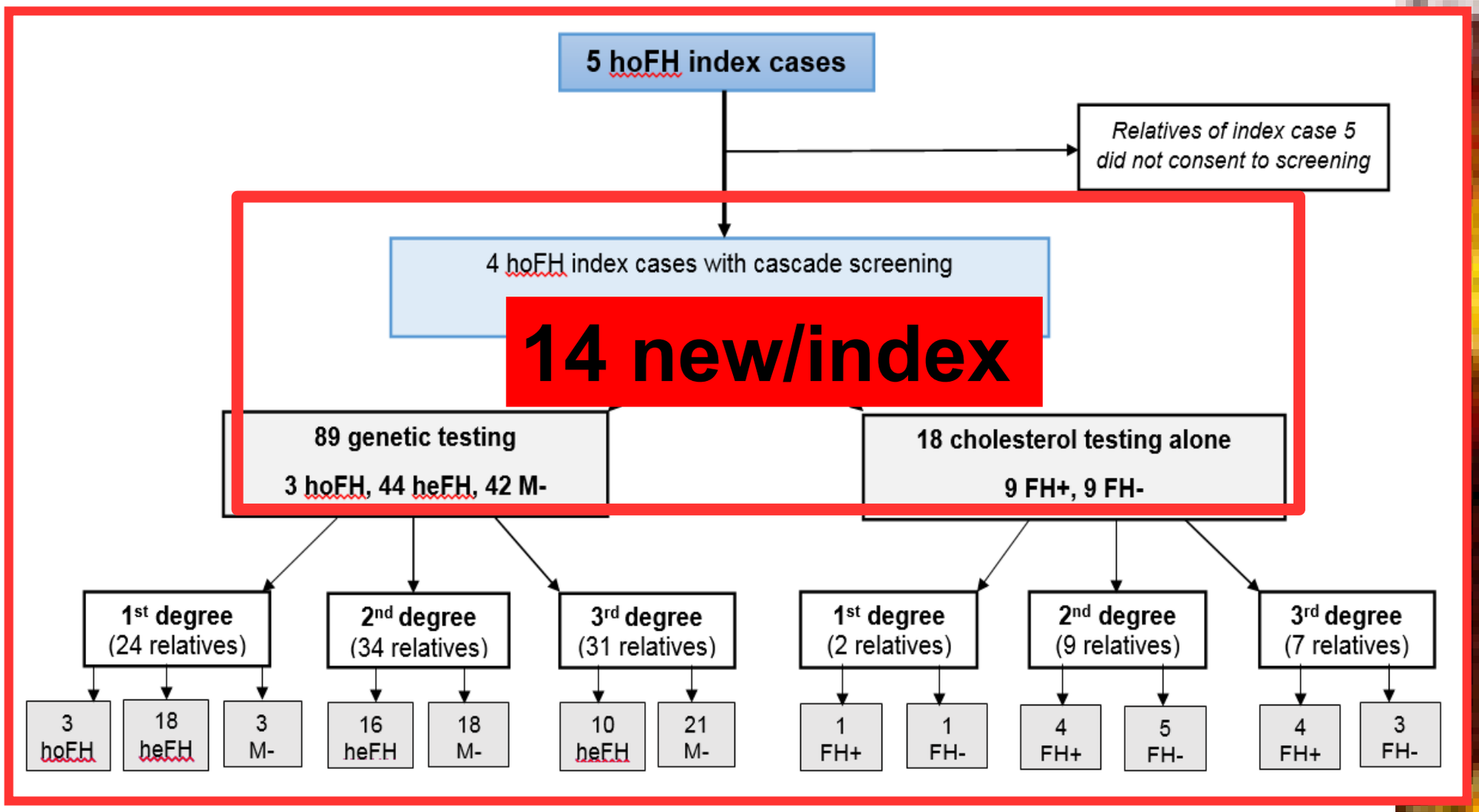
Schematic Describing Reverse Cascade Screening Using Genetic Testing[3]



Reverse cascade screening is an effective method for population screening for FH

1. Morris JK, et al. *Am J Med Genet* 2012;158A:78-84. 2. Wald DS, et al. *BMJ*. 2007;335:599. 3. Wu X, et al. *Clinical Cardiology*. 2017;40:1169–1173.

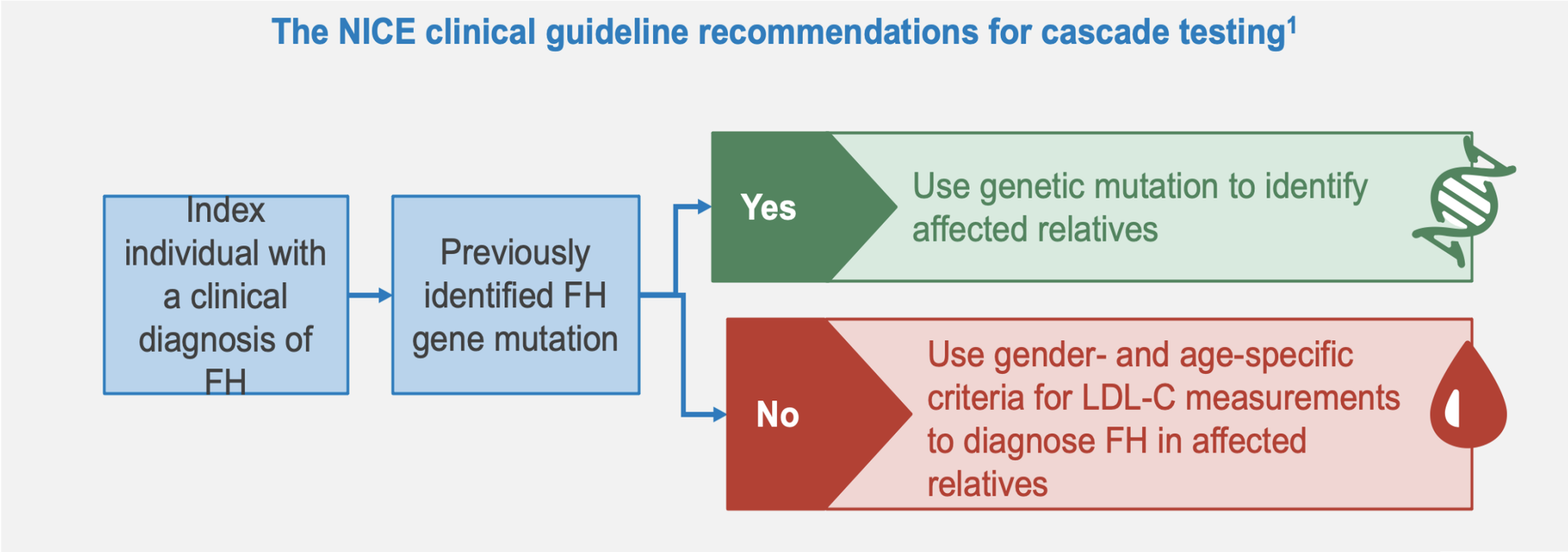
Vietnam: Forward cascade testing



Truong et al 2018 Vietnam National Heart Institute

NICE Guideline Recommendations for the Implementation of Cascade Screening

- The Centers for Disease Control have classified FH as a Tier 1 condition for cascade screening with recommended implementation outlined in the NICE Guideline for identification and management of FH[1]



NICE recommends against using the SBR criteria for case detection of relatives of a patient, as this results in under-diagnosis. Instead, NICE recommends genetic testing or age- and gender-specific LDL-C measurements when a genotypic result is not available to the patient

1. O'Brien EC, et al. *Am Heart J.* 2014;167(3):342-349. 2. Henderson R, et al. *J Biomed Sci.* 2016;23:39. doi: 10.1186/s12929-016-0256-1.

Recognizable Latent or Early Symptomatic Stage

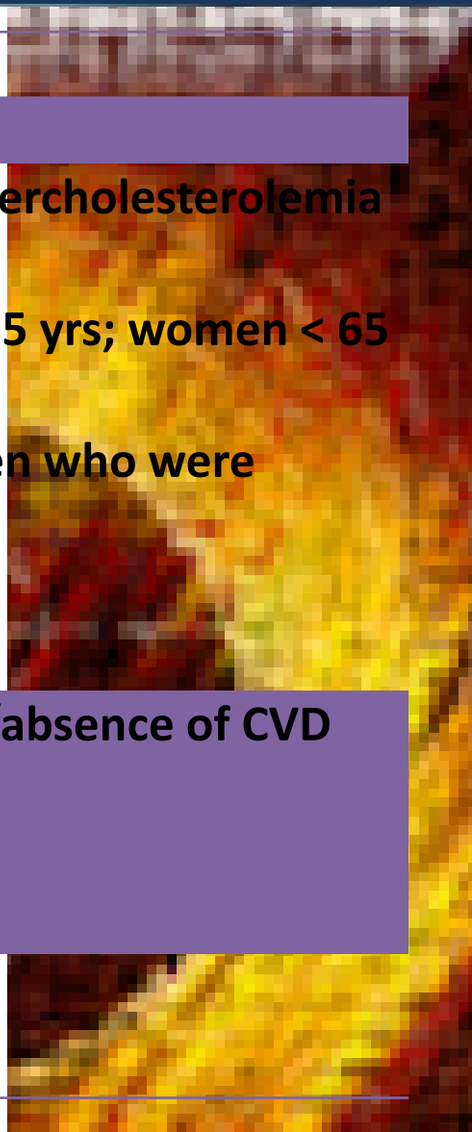
1. Children and young adults with FH are rarely symptomatic.
2. While CVD typically manifests in adulthood, the process begins in childhood.
3. Identifying children is critical to reducing the burden of disease in adulthood.
4. Some, but not all, guidelines underscore the value of noninvasive imaging of atherosclerosis (e.g. cIMT) in assessing and managing asymptomatic FH subjects.

What Age To Screen?

Cholesterol Screening

Age	Type	Criteria
≥ 2 yrs of age	Selective	• 1 or both biologic parents known to have hypercholesterolemia or are receiving LLM; or • Family history of premature CVD (i.e. men < 55 yrs; women < 65 yrs); or • Whose family history is unknown (e.g. children who were adopted).
≥ 10 yrs of age*	Universal	• Regardless of general health or the presence/absence of CVD risk factors. • If normal, repeat every 5 yrs.

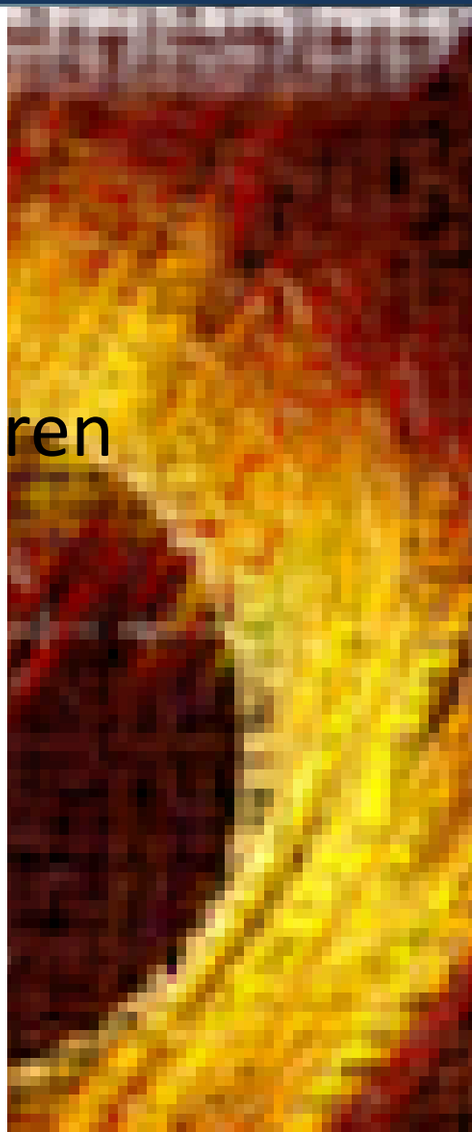
*Selective screening if clinically indicated.
LLM = lipid-lowering medications; CVD = cardiovascular disease
National Lipid Association Annual Summary of Clinical Lipidology 2017. J of Clinical Lipidology (2016) , S1-S50



Family History

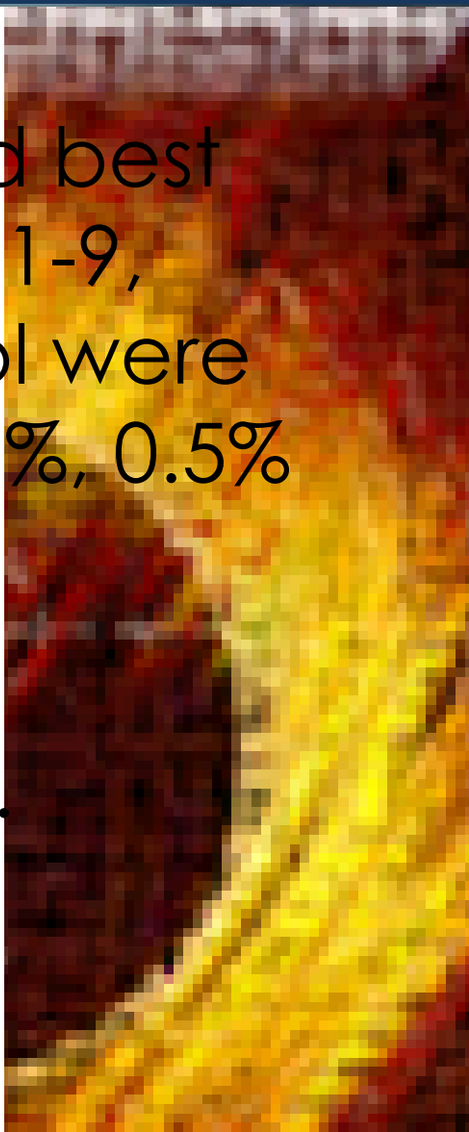
Reliance on family history alone as a basis for lipid screening fails to identify as many as 30-60% of children and adolescents with elevated levels of cholesterol.

Dennison 1989, Griffin 1989, Freedman 1992



Meta-analysis on child-parent screening for FH (13 studies, 1,907 cases, 16,221 controls)

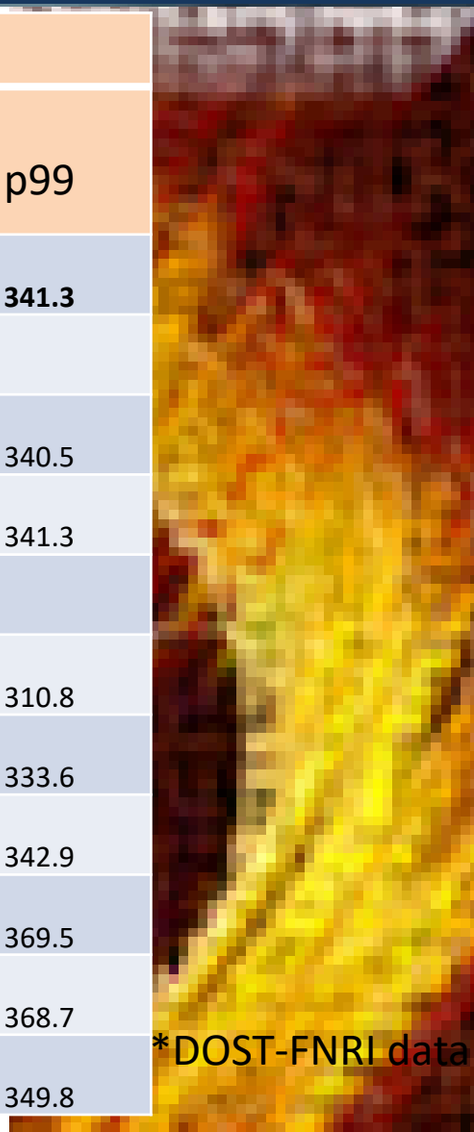
- Serum cholesterol concentration discriminated best between people with and without FH at ages 1-9, when the detection rates with total cholesterol were 88%, 94% and 96% for false positive rates of 0.1%, 0.5% and 1%.
- Results were similar with LDL cholesterol.
- Screening newborns were much less effective.



Wald David S, Bestwick Jonathan P, Wald Nicholas J. Child-parent screening for familial hypercholesterolaemia: screening strategy based on a meta-analysis BMJ 2007; 335 :599

Mean and Percentile Distribution of Total Cholesterol Level Among Adults ≥ 20 years old by Sex and Age Group: Philippines, 2013*

Sex / Age group	n	Mean	Min	Max	Percentile distribution			
					p50	p90	p95	p99
All	**19010**	**201.8**	**13.1**	**669.1**	**196.9**	**261.4**	**284.2**	**341.3**
Sex								
Male	8906	195.8	13.1	559.9	191.1	253.7	276.8	340.5
Female	10104	206.9	43.2	669.1	201.9	266.8	290.4	341.3
Age group								
20-29 years old	4073	187.1	67.2	431.7	182.2	241.7	**259.9**	310.8
30-39 years old	3641	197.8	20.5	486.9	194.2	252.5	273.4	333.6
40-49 years old	4175	204.8	13.1	474.5	200.8	261.4	280.3	342.9
50-59 years old	3530	216.9	18.6	669.1	212.7	280.3	304.3	369.5
60-69 years old	2108	216.3	25.5	630.9	212.4	281.5	303.9	368.7
70 years old and above	1483	208.8	73.4	533.6	205.4	271.4	295.4	349.8

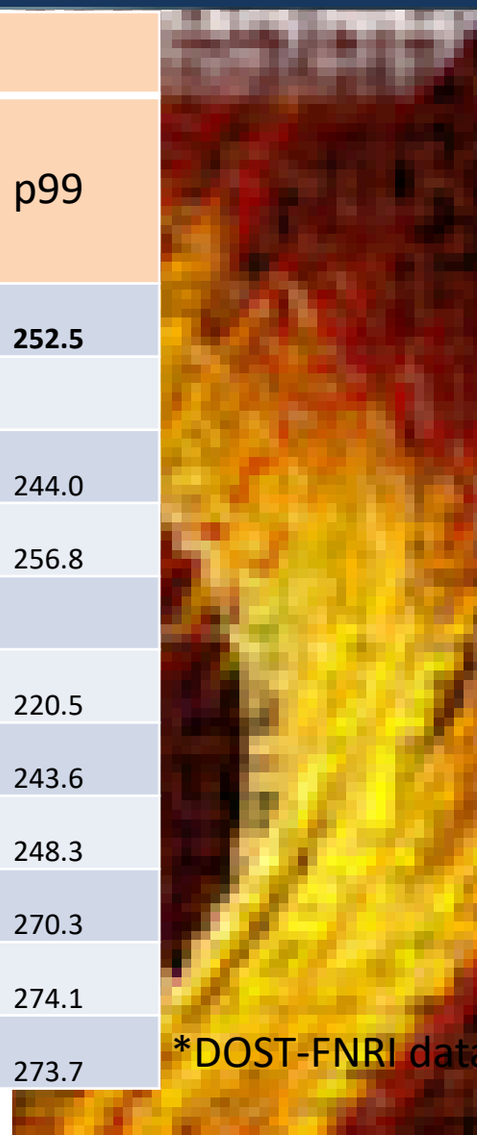


*DOST-FNRI data

Mean and Percentile Distribution of LDL-C Level Among Adults ≥ 20 years old by Sex and Age Group: Philippines, 2013*

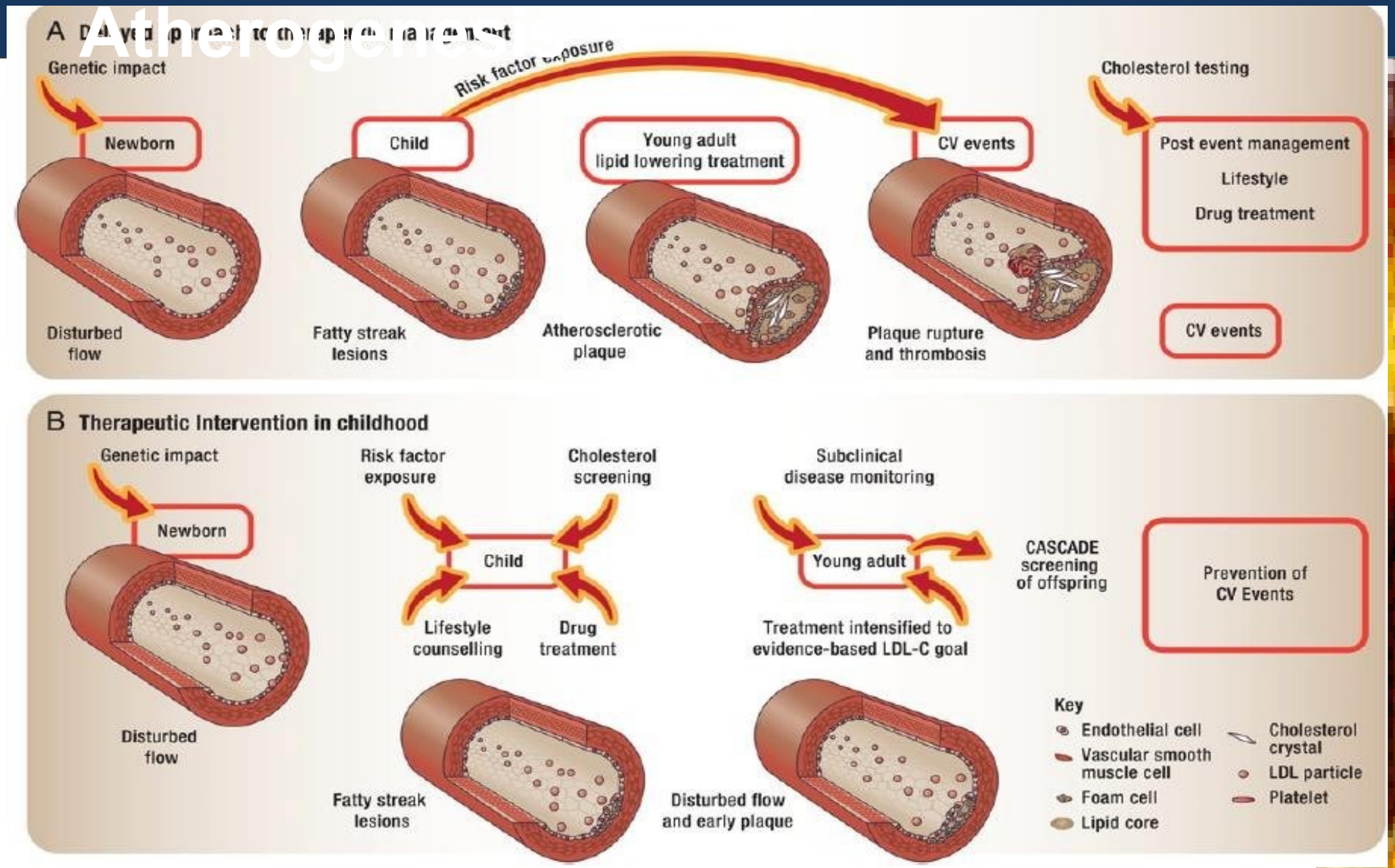
Cholesterol Dilemma

Sex / Age group	n	Mean	Min	Max	Percentile distribution			
					p50	p90	p95	p99
All	**19002**	**131.5**	**1.5**	**525.9**	**127.8**	**185.3**	**205.0**	**252.5**
Sex								
Male	8898	123.9	4.3	467.2	120.5	176.1	193.8	244.0
Female	10104	138.0	1.5	525.9	133.6	191.9	212.0	256.8
Age group								
20-29 years old	4070	117.3	24.3	340.2	113.5	162.9	**181.1**	220.5
30-39 years old	3639	127.7	12.0	397.3	124.7	176.5	194.6	243.6
40-49 years old	4173	134.0	4.3	361.4	131.3	184.6	202.7	248.3
50-59 years old	3529	145.4	1.5	525.9	142.9	203.5	225.9	270.3
60-69 years old	2108	145.9	8.5	498.8	142.1	202.7	225.9	274.1
70 years old and above	1483	141.8	5.8	410.4	137.1	196.5	222.4	273.7



*DOST-FNRI data

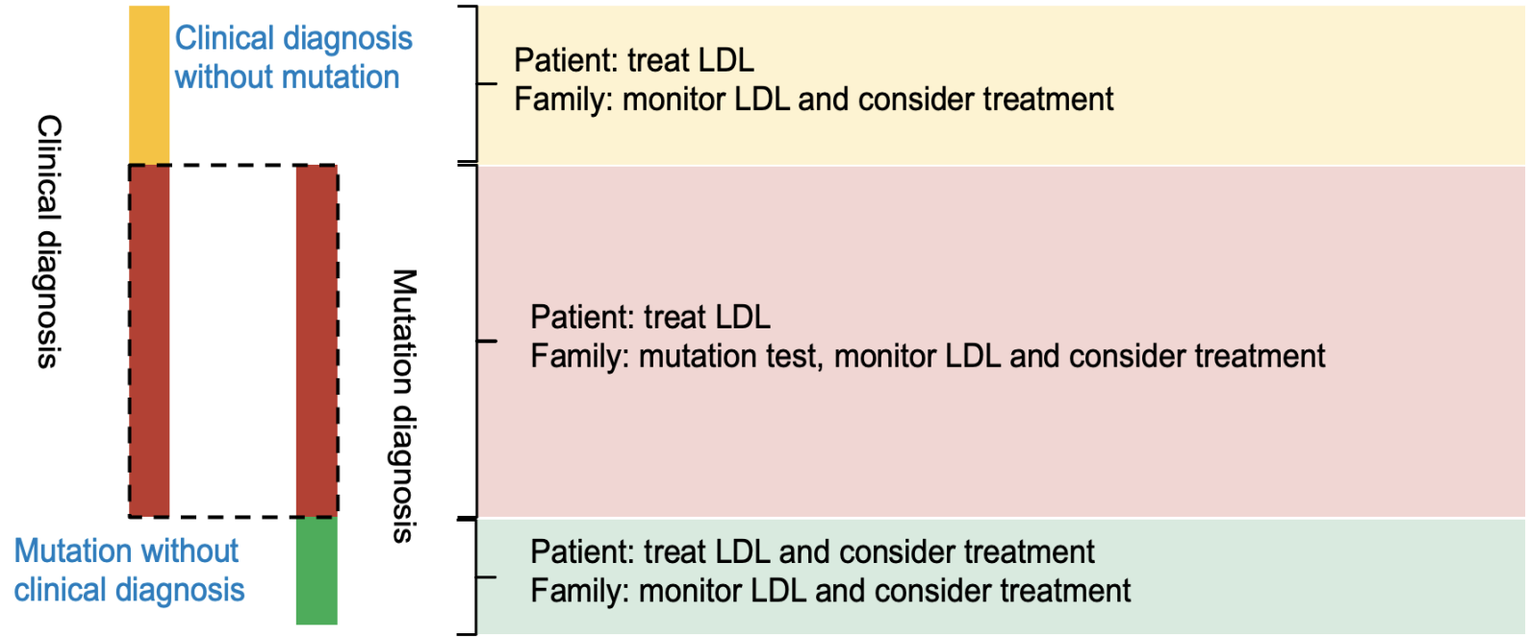
Time Course of Human Atherogenesis



European Heart Journal (2015) **36**, 2425–2437

Genetic Testing Is A Complimentary Tool for Diagnosing FH

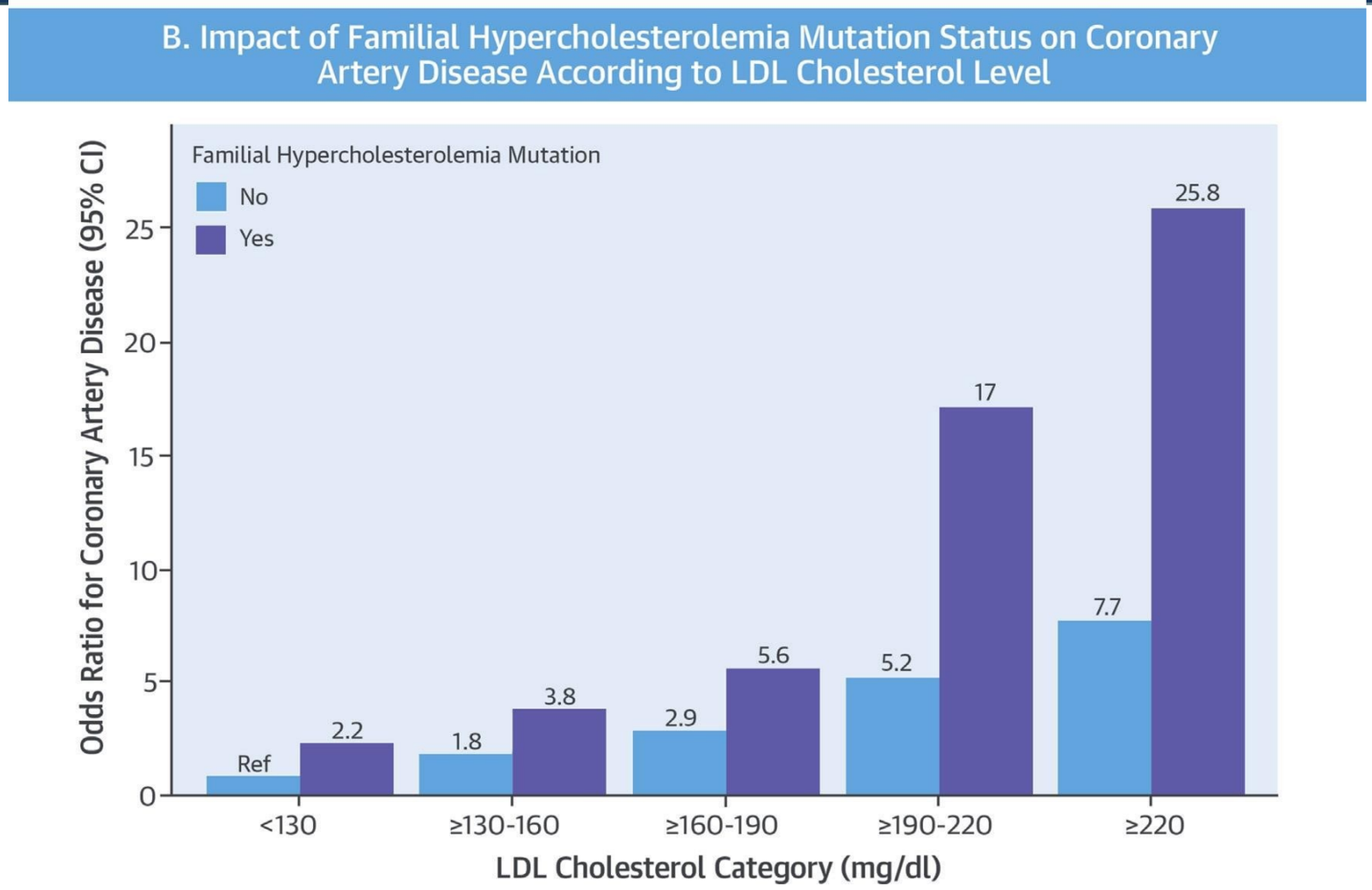
- Although clinical diagnosis criteria has been extensively used for FH, genetic testing is the preferred method for FH as it provides an unequivocal diagnosis[1]
- The variability of FH disease severity between genes and within each gene limits the ability to characterize patients' genotype based on clinical features alone[2]
- **Genetic testing only screens for the most common mutations (*LDLR*, *APOB*, *PCKS9*) associated with FH[3]**
- **Depending on referral criteria, 10–40% of those with a clinical diagnosis may not have a causal mutational diagnosis[3]**



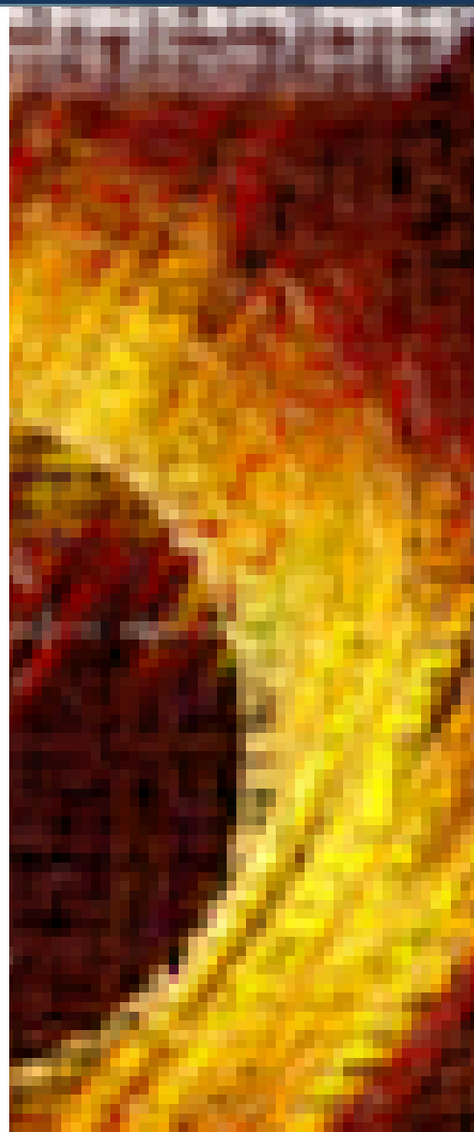
As the clinical phenotype of FH is hughly variable, mutational diagnosis of patients may determine treatment strategies and screening of family members

1. De Castro-Orós I, et al. *Appl Clin Genet*. 2010;3: 53-64. 2. Foody JM, et al. *J Clin Lipidol*. 2016;10:970-986. 3. Nordestgaard BG, et al. *Eur Heart J*. 2013;34:3478-3490.

FH mutation presence and CAD risk



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



The Genetics and Screening of Familial Hypercholesterolemia

Raymond Henderson[1], Maurice O'Kane[2], Victoria McGilligan[1] and Steven Watterson[1*]

Abstract

Familial Hypercholesterolaemia is an autosomal, dominant genetic disorder that leads to elevated blood cholesterol and a dramatically increased risk of atherosclerosis. It is perceived as a rare condition. However it affects 1 in 250 of the population globally, making it an important public health concern. In communities with founder effects, higher disease prevalences are observed.

We discuss the genetic basis of familial hypercholesterolaemia, examining the distribution of variants known to be associated with the condition across the exons of the genes *LDLR*, *ApoB*, *PCSK9* and *LDLRAP1*. We also discuss screening programmes for familial hypercholesterolaemia and their cost-effectiveness. Diagnosis typically occurs using one of the Dutch Lipid Clinic Network (DCLN), Simon Broome Register (SBR) or Make Early Diagnosis to Prevent Early Death (MEDPED) criteria, each of which requires a different set of patient data. New cases can be identified by screening the family members of an index case that has been identified as a result of referral to a lipid clinic in a process called cascade screening. Alternatively, universal screening may be used whereby a population is systematically screened.

It is currently significantly more cost effective to identify familial hypercholesterolaemia cases through cascade screening than universal screening. However, the cost of sequencing patient DNA has fallen dramatically in recent years and if the rate of progress continues, this may change.

Keywords: Familial hypercholesterolaemia, FH, cascade screening, screening, cholesterol, universal screening, atherosclerosis, CVD, CHD

Henderson *et al. Journal of Biomedical Science* (2016) 23:39
DOI 10.1186/s12929-016-0256-1

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Journal of Biomedical Science

REVIEW

Open Access

Cascade Screening Based on Genetic Testing Is Cost-Effective : Evidence for the Implementation of Models of Care for Familial Hypercholesterolemia

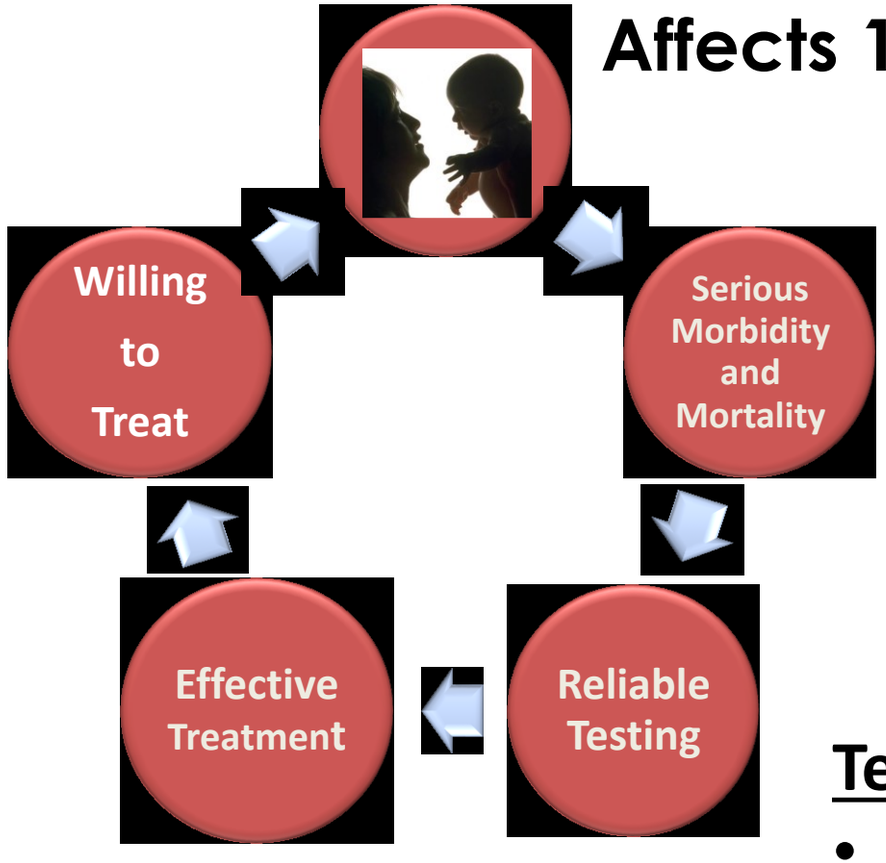
Zanfina Ademi, MPharm, MPH, PhD*, Gerald F. Watts, DSc, PhD, DM, FRCP, FRACP, Jing Pang, PhD, Eric J. G. Sijbrands, MD, PhD, Frank M. van Bockxmeer, PhD, MHGSA, FFSc (RCPA), FAHA, Peter O'Leary, BSc, PhD, MAACB, ARCPA, FFSc (RCPA), Elizabeth Geelhoed, PhD, Danny Liew, MBBS, FRACP, PhD

RESULTS: The model estimated that screening for FH would reduce the 10-year incidence of CHD from 50.0% to 25.0% among people with FH. Of every 100 people screened, there was an overall gain of 24.95 life-years and 29.07 quality-adjusted life years (discounted). The incremental cost-effectiveness ratio was in Australian dollars, $4155 per years of life saved and $3565 per quality-adjusted life years gained.

CONCLUSION: This analysis within an Australian context, demonstrates that cascade screening for FH, using genetic testing supplemented with the measurement of plasma low-density lipoprotein cholesterol concentrations and treatment with statins, is a cost-effective means of preventing CHD in families at risk of FH.

J Clin Lipidol 2014; 8: 390-400.

Principles of Screening Congenital Hypothyroidism



Affects 1:4000 newborns

Shared Decision
- Physician
- Parent

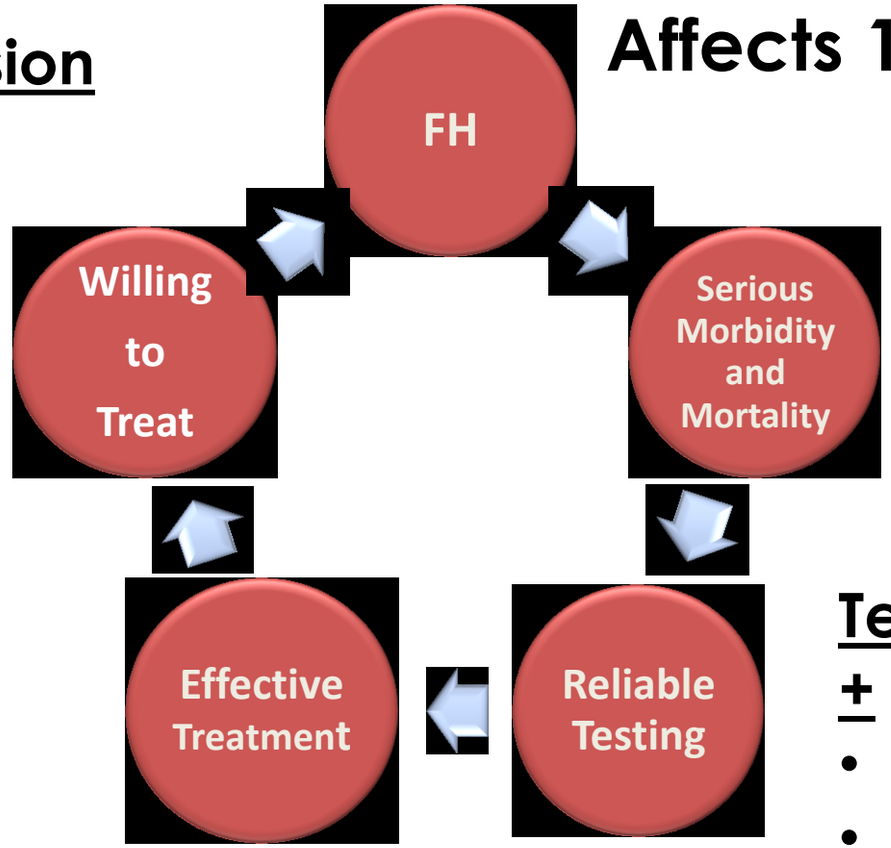
Increased Risk
- Developmental Delay
- Mental Retardation

Treatment
- Thyroid Hormone
- 10-15 mcg/kg/d
- Reliable monitoring

Testing - TSH
- Reliable
- Specific

Principles of Screening
Familial Hypercholesterolemia

Shared Decision
- Physician
- Parent



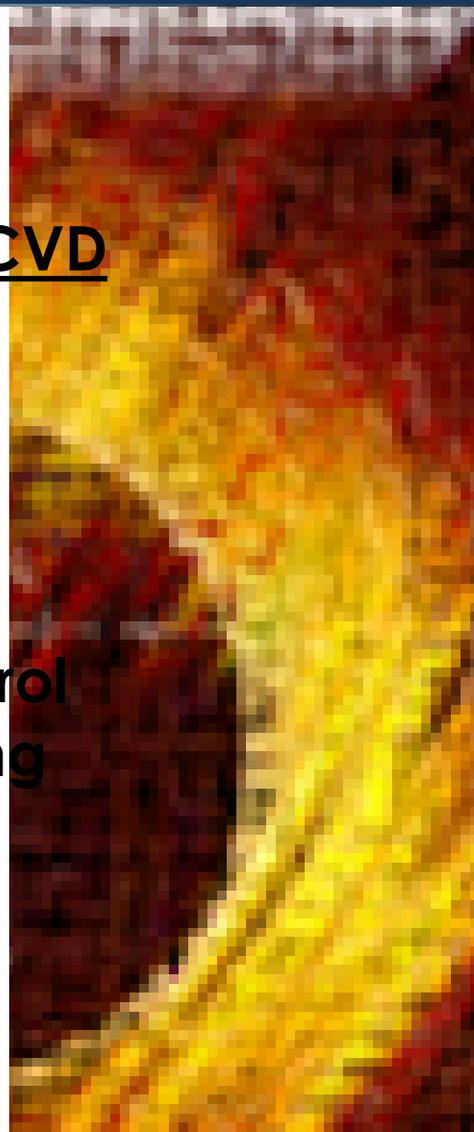
Affects 1:250

Premature CVD
- MI
- CVA
- Death

LLMs
- Statins
- Ezetimibe
- BAS
- New agents*

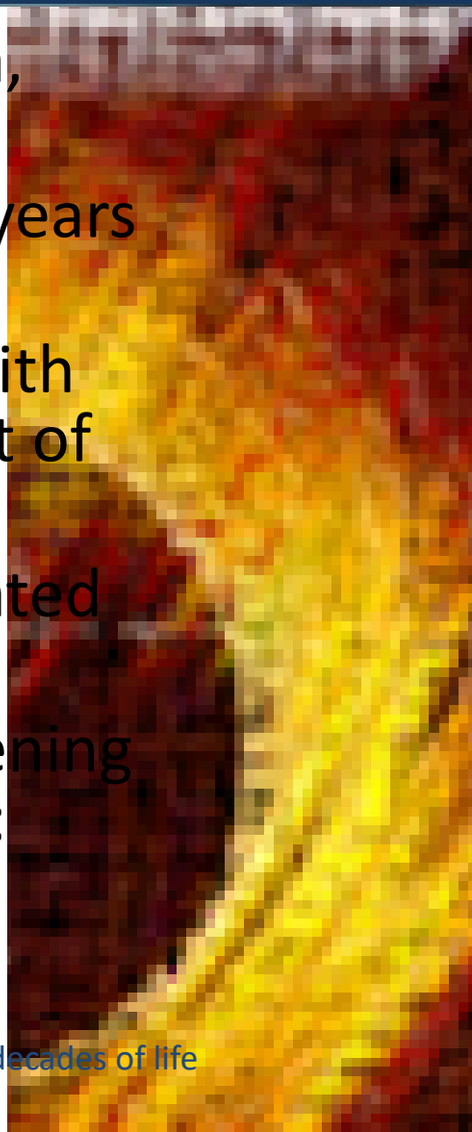
Tests - Cholesterol
± Genetic Testing
- Reliable
- Accurate
- Accessible
- Inexpensive

* Not FDA approved <18 yr



Some thoughts…

- There is no generally accepted screening program for children, adolescents, and young adults.
- Universal screening, started at age 10 and continued every 5 years thereafter, may help simplify the process for busy clinicians.
- Early recognition of a child or young adult with FH, coupled with therapy from a young age, will impede, if not arrest, the onset of atherosclerosis.
- Statin therapy alone could potentially avert 96-98% of FH-related CHD deaths in individuals < 40 years of age.
- Identification of a child with FH combined with effective screening of 1st and 2nd degree relatives (i.e. reverse cascade screening):
  - Combines the benefits of universal + cascade screening.
  - Has the potential, within 1 generation, of detecting all cases of FH.



Wiegman A, Gidding SS, et al. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. Eur Heart J. 2015;36(36):2425–37.

WHO Call to Action on FH – 2020

- Awareness – public, patient, medical community
- Advocacy – FH in children unrecognized…
- Screening, testing, diagnosis – cascade, universal
- Treatment – unrestricted access
- Severe and homozygous FH – very high risk
- Family-based care – integrated care needed
- Registries – essential, require sustained funding
- Research – basic science, genetic, epidemiologic, clinical
- Cost and value – understand value in FH care

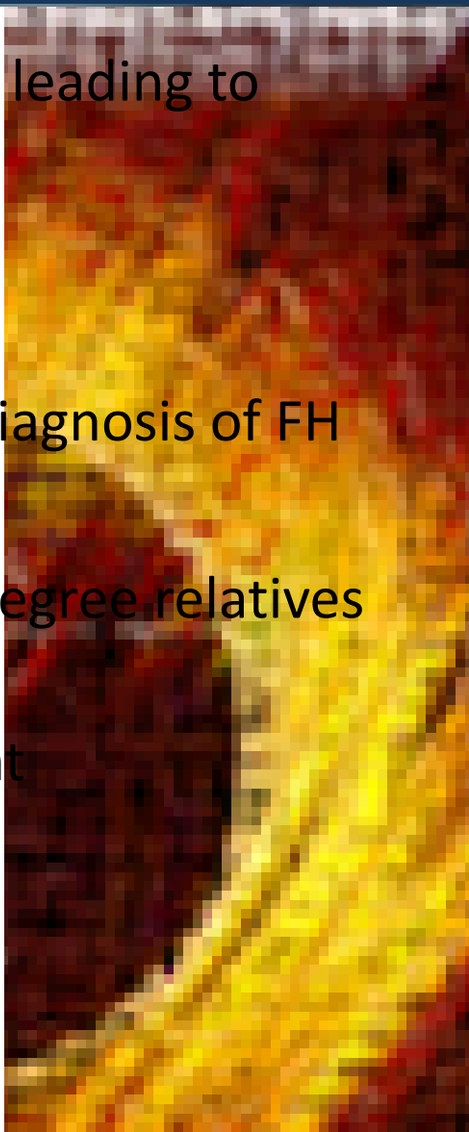
JAMA Cardiol 2020, published online 01/02/20

Our Hope…

- Identify FH suspects and do cascade screening
- Enroll FH suspects in FH Registry to have our national data
- Include lipid profile of children in national surveys
- Find out 95th percentile of total cholesterol and LDL cholesterol in children
- Do universal or selective cholesterol screening of children at 5-10 years old
- Do universal cholesterol screening of college applicants (expected mean age of 18 years old)

CONCLUSION

- FH is an inherited genetic disorder manifesting with very high levels of LDL-C leading to premature atherosclerosis and early death
- FH is often unrecognized or underdiagnosed
- Unique phenotypic features can help identify FH suspects
- The DLCN criteria has been adopted or modified by many countries for the diagnosis of FH
- Screening can be done by universal, selective or cascade method
- Cascade screening from a proband can help identify other first and second-degree relatives with FH who are often unaware of their condition
- Genetic testing to identify mutations is ideal but not an absolute requirement
- Cascade screening has been proven to be cost effective
- Let us all help to establish a FH registry for the Philippines
- Consider strongly screening children and college applicants (young adults)



Familial Hypercholesterolemia for the Filipino Heart (FH^2)

THANK YOU for your kind attention