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The Importance of Pediatric Lipid Testing in the Diagnosis and Treatment of Familial Hypercholesterolemia

Outline

- FH through the lens of one family's experience
- Familial Hypercholesterolemia
    - Genetic causes, frequency, transmission
    - CV risk if untreated
    - Recommended pediatric screening
    - Current frequency of screening
    - Benefits of early treatment
    - Lipid altering therapies in FH
- Back to Jane
- Why does an FH diagnosis matter?
- Why is screening controversial?
- What needs to change: for providers, for parents
- Special guest – Lisa Khalafi

Learning Objectives

- Describe the specific genetics of FH and the benefits of early treatment of hypercholesterolemia associated with this genetic disorder.
- Examine the role of cascade screening in the diagnosis of FH.
- Identify the barriers to implementing universal pediatric lipid screening.
- Analyze the value of point of care (POC) lipid testing in pediatric offices – allowing parents and children to avoid a trip to a laboratory.

Jane B

- 1987: Jane B is a 39-year-old woman

- No past medical history – nonsmoker, BMI ~25, no HTN, no diabetes, 2 normal vaginal deliveries
    - Developed chest pressure and SOB while raking leaves
    - Noted left arm pain and SOB while climbing stairs
    - Driving to work developed severe “heartburn”, nausea, tightness in her chest
    - Colleagues at work told her she looked “gray”
    - Husband brought her to the ER

Jane B

- Jane was diagnosed with a heart attack
- Catheterization reveals multivessel disease and she underwent bypass surgery

- What do you want to know?

Jane B: Lipid panel from the ER

- Total cholesterol: 420 mg/dL
- LDL-C: 350 mg/dL
- HDL-C: 50 mg/dL
- Triglycerides: 100 mg/dL

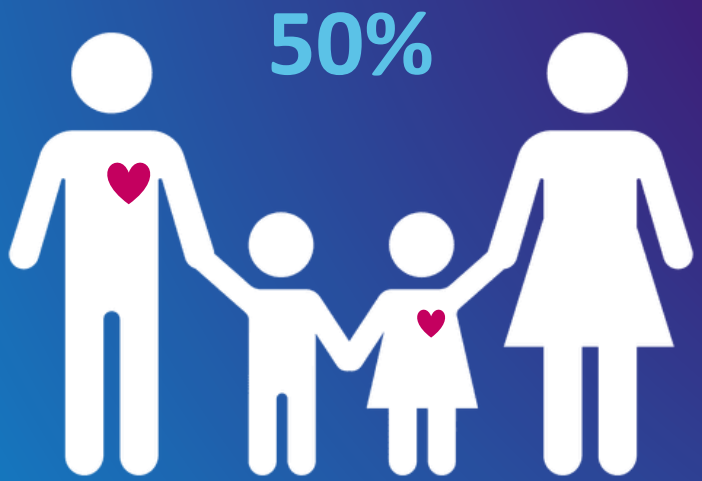
- What else do you want to know?

Jane B: Family history

- Jane was 19 when her mother died of a heart attack at age 43
- Her maternal grandmother died at age 39 also of a heart attack
- Yet Jane never considered herself at risk – even as she was headed to the ER

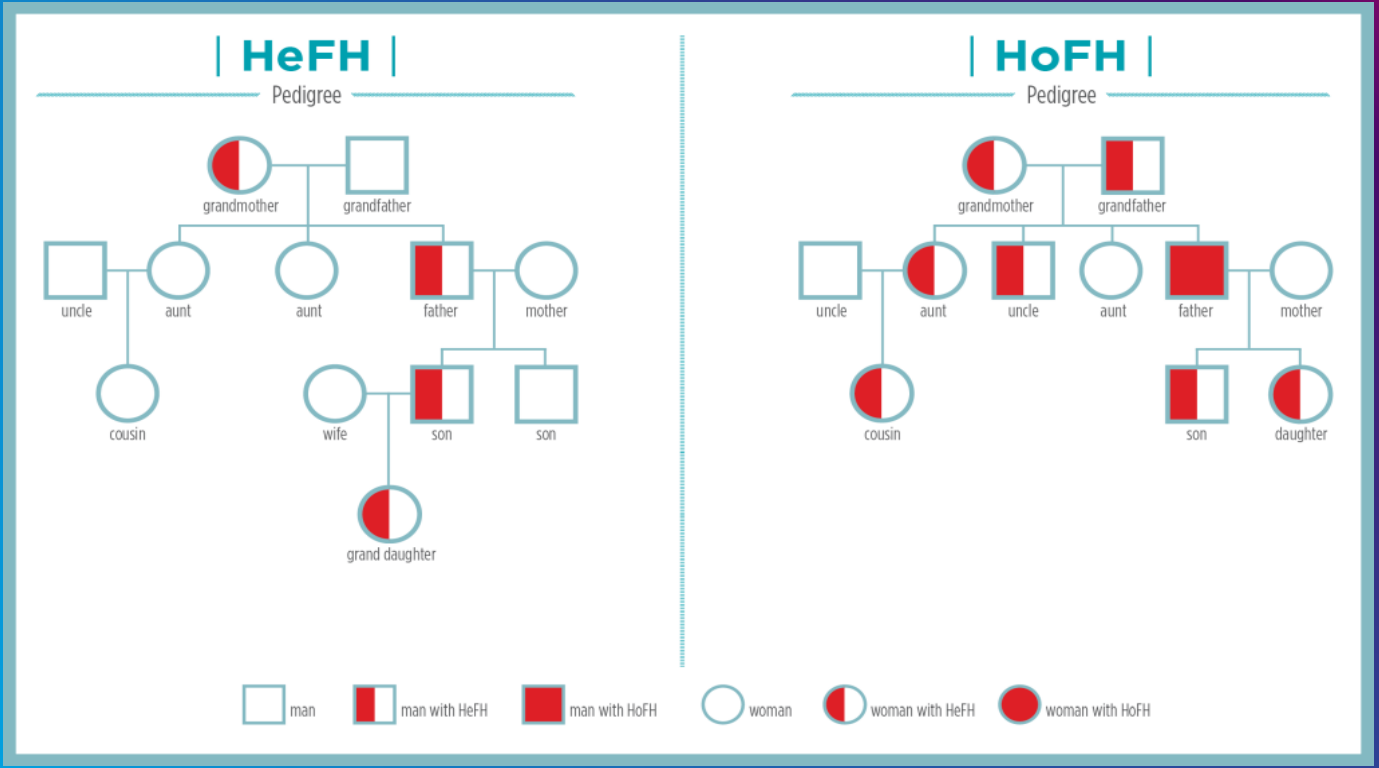
Autosomal dominant genetic disorder

Pictured below: Heterozygous FH (HeFH)



If YOU have FH, each of your CHILDREN has a **50% chance** of inheriting FH.

FH runs in families

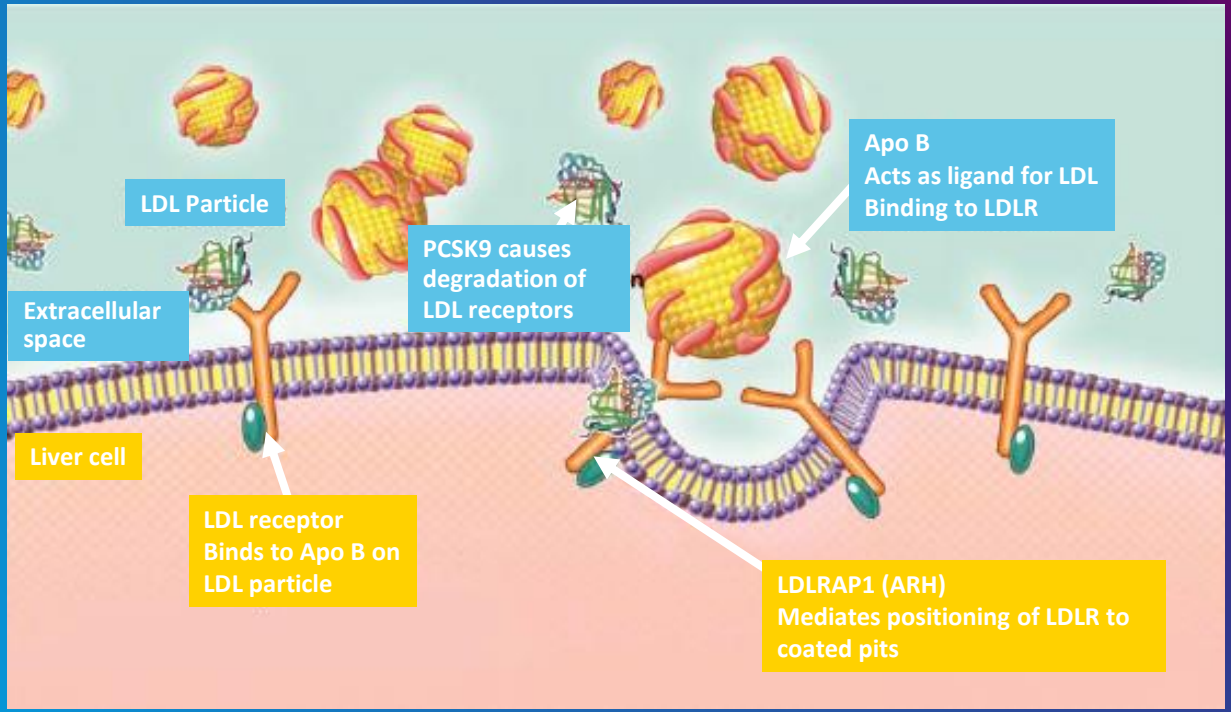


Two forms of FH

HeFH	1 gene	>190 mg/DL	30-60 years	Most respond to drug therapy	Common 1 in 250
HoFH	2 genes	>400 mg/DL	childhood	Poor response to drug therapy	Rare 1 in 300,000

CHD onset

Four known FH genes: LDLR, APOB, PCSK9, LDLRAP1



Sniderman A, et al JACC 2014

Familial Hypercholesterolemia

- Occurs in 1:250 people worldwide
- Autosomal dominant disorder meaning half of their first-degree relatives will also have FH[1]
- People with FH universally require medications to lower their cardiac risk[1]

J Am Coll Cardiol. 2018;72:662-680

Markedly elevated LDL-C: think familial hypercholesterolemia

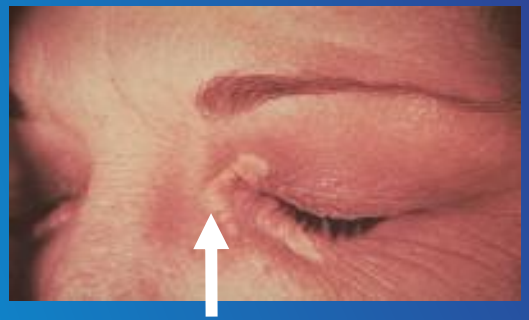
- Adults with an untreated LDL-C $\geq$ 190 mg/dL and children with an untreated LDL-C $\geq$ 160 mg/dL[1]

- Untreated 50% of men will have had a cardiac event by 50 and 30% of women will have had a cardiac event by 60[2]

- 90% of affected individuals will experience ASCVD if untreated secondary to prolonged exposure to elevated cholesterol[3]

1.Journal of Clinical Lipidology. 2011;5:2-15
2.Circulation 1974;49:476-88
3.Circulation. 2015;132:2167-2192

Manifestation of familial hypercholesterolemia in adults



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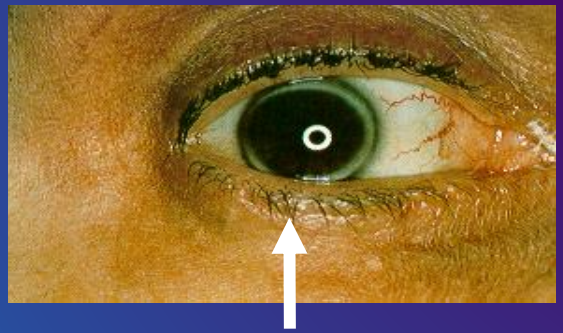

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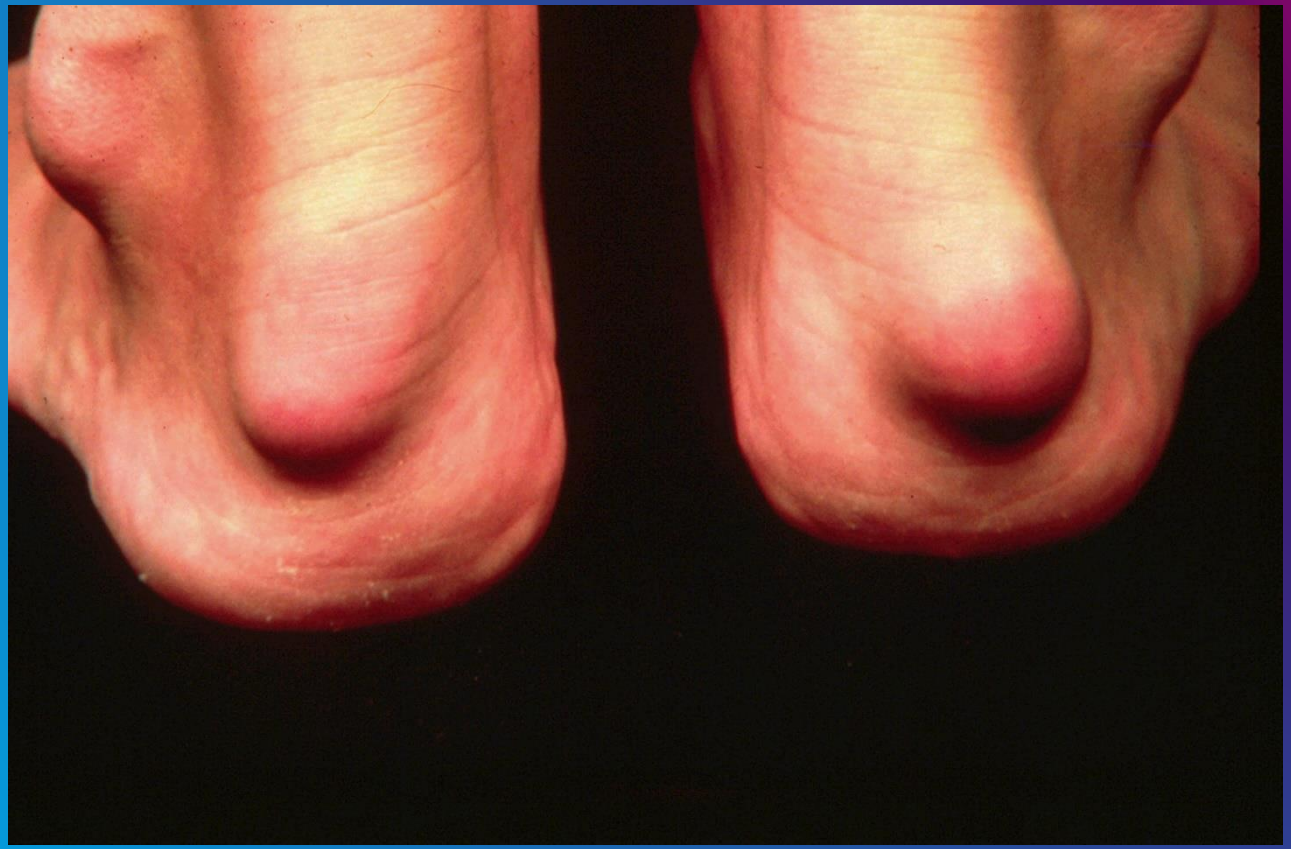


Universal pediatric screening: 2011 recommendations

The American Academy of Pediatrics

NIH: National Heart, Lung, and Blood Institute

Universal screening recommendations:

- All children between the ages of 9-11 and again at 17-21
- Children with family member with FH, or family history of heart disease, at age 2

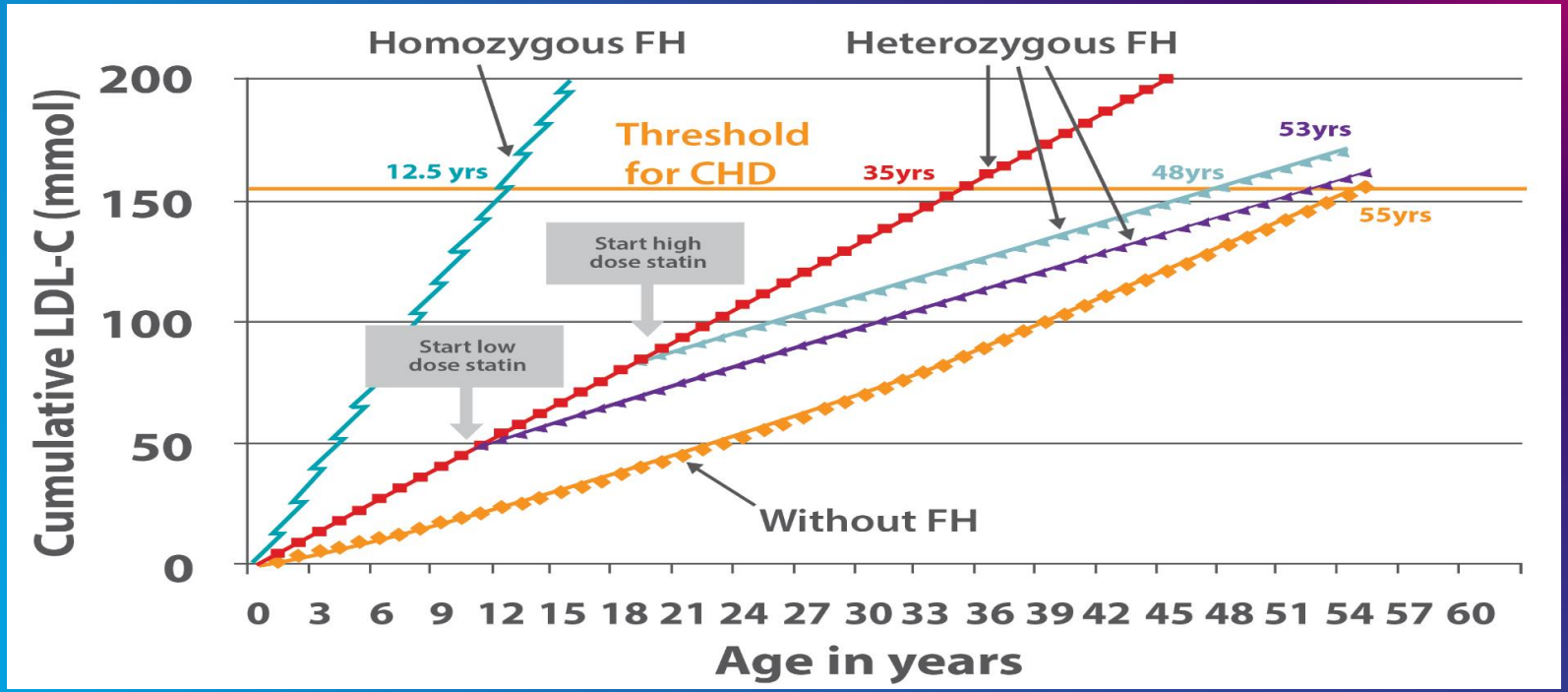
Year	Universal Pediatric Screening Recommended	Insufficient Evidence for Universal Pediatric Screening
2011	National Heart Lung Blood Inst	
2011	American Academy of Pediatrics	
2011	National Lipid Association	
2016		US Preventive Services Task Force
2018	American Heart Association	
2018	American College of Cardiology	
2018	Am Association of CV and P Rehab	
2018	Am Academy of Physicians Assist	
2018	Assoc of Black Cardiologists	
2018	Am College of Prevent Medicine	
2018	American Diabetes Assoc	
2018	American Pharmacists Assoc	
2018	American Society of Prevent Car	
2018	National Lipid Association	
2018	Preventive CV Nurses Association	

Current frequency of lipid screening

- Published data suggests only ~4-5% of children between the ages of 9-11 year are screened[1]

1. Journal of Clinical Lipidology (2020) doi: https://doi.org/10.1016/j.jacl.2020.01.013

An opportunity for prevention



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

Medications to lower LDL Cholesterol

To lower LDL-Cholesterol

- Statins
  - lovastatin (Mevacor) 10-80 mg/day
  - atorvastatin (Lipitor) 10 - 80 mg/day
  - rosuvastatin (Crestor) 5 - 40 mg/day
  - simvastatin (Zocor) 5 – 40 mg/day
  - pravastatin (Pravachol) 10 – 80 mg/day
  - fluvastatin (Lescol) 20 – 80 mg/day
  - pitavastatin (Livalo) 1- 4 mg/day

- Ezetimibe (Zetia) 10 mg/day (blocks Niemann-Pick C-1 Like1 receptor – blocks sterol absorption and upregulates LDL R)

1. Journal of Clinical Lipidology. 2011;5:38-45
2. Circulation. 2019;139:e1046-e1081

Medications to lower LDL-Cholesterol

To lower LDL-Cholesterol

- PCSK9 Inhibitors
  - Alirocumab (Praluent) 75 or 150 mg every 14 days
  - Evolocumab (Repatha) 140 mg every 14 days or 420 mg every month

Jane’s lipid-altering therapy

- Prescribed lovastatin, simvastatin, atorvastatin and eventually rosuvastatin

- Ultimately only able to tolerate rosuvastatin at 10 mg – ezetimibe was added when it came on the market in 2002

Jane’s lipid panel on rosuvastatin and ezetimibe /CV events

- Total cholesterol: 235 mg/dL
- LDL-C: 158 mg/dL
- HDL-C: 54 mg/dL
- Triglycerides: 115 mg/dL
- Subsequent cardiac events:
  - Second heart attack in 2005
  - Two strokes – no residual ~2007
- Alirocumab added in 2015

Jane’s lipid panel on rosuvastatin, ezetimibe & alirocumab

- Total cholesterol: 130 mg/dL
- LDL-C: 52 mg/dL
- HDL-C: 56 mg/dL
- Triglycerides: 110 mg/dL

Why Does the Diagnosis of FH Matter?

FH impacts families

FH has been recognized by the Centers of Disease Control Office of Public Health Genomics as a tier 1 genetic disorder – meaning that there is strong evidence for health benefits related to diagnosis/treatment of FH. As such, implementing case finding via family history-based screening, cascade screening and other strategies such as universal screening of children is indicated.[1]

1.Circulation. 2015;132:2167-2192

Cascade screening

- Involves either genetic testing or lipid screening in all first-degree relatives of an index case and repeating this with newly identified patients[1]

- Cascade screening has been found to be extremely cost effective[1]

J Am Coll Cardiol 2018;72:662-80

Why is pediatric lipid screening controversial?

USPSTF cholesterol screening recommendation: children

Population	Recommendation	Grade
Children and adolescents 20 years or younger	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for lipid disorders in children and adolescents 20 years or younger.	I

JAMA 2016.316(6):645-445

Lipid Screening in Childhood and Adolescence for Detection of Familial Hypercholesterolemia

Evidence Report and Systematic Review for the US Preventive Services Task Force

- **Conclusions and Relevance:** Screening can detect FH in children, and *lipid-lowering treatment in childhood can reduce lipid concentrations in the short term, with little evidence of harm. There is no evidence for the effect of screening for FH in childhood on lipid concentrations or* cardiovascular outcomes in adulthood, or on the long-term benefits or harms of beginning lipid-lowering treatment in childhood.

JAMA 2016.316(6):645-445

ORIGINAL ARTICLE

20-Year Follow-up of Statins in Children with Familial Hypercholesterolemia

Ilse K. Luirink, M.D., Albert Wiegman, M.D., Ph.D., D. Meeike Kusters, M.D., Ph.D., Michel H. Hof, Ph.D., Jaap W. Groothoff, M.D., Ph.D., Eric de Groot, M.D., Ph.D., John J.P. Kastelein, M.D., Ph.D., and Barbara A. Hutten, Ph.D.

METHODS

We report a 20-year follow-up study of statin therapy in children. A total of 214 patients with familial hypercholesterolemia (genetically confirmed in 98% of the patients), who were previously participants in a placebo-controlled trial evaluating the 2-year efficacy and safety of pravastatin, were invited for follow-up, together with their 95 unaffected siblings. Participants completed a questionnaire, provided blood samples, and underwent measurements of carotid intima–media thickness. The incidence of cardiovascular disease among the patients with familial hypercholesterolemia was compared with that among their 156 affected parents.

CONCLUSIONS

In this study, initiation of statin therapy during childhood in patients with familial hypercholesterolemia slowed the progression of carotid intima–media thickness and reduced the risk of cardiovascular disease in adulthood. (Funded by the AMC Foundation.)

N ENGL J MED 381;16 NEJM.ORG OCTOBER 17, 2019

Pediatric lipid profiles

	Acceptable	Borderline	High
Total Cholesterol	< 170	170-199	>200
LDL-Cholesterol	< 110	110-129	>130
HDL-Cholesterol	>45	40-45	<40 low
Triglycerides 0-9 years	<75	75-99	>100
Triglycerides 10-19 years	<90	90-129	>130

Why aren't pediatricians screening children?

- Only 26% knew about the NHLBI /AAP 2011 recommendations
- 68% reported never/rarely or sometimes screened healthy 9-11 year olds
- Reasons for screening: family history of heart disease (61%) or childhood obesity (82%)
- Although 62% and 89% believed statins were appropriate for children with elevated LDL unresponsive to lifestyle, only 8-21% felt comfortable initiating statins (lack of local specialists)

J Pediatr 2017;185:99-105

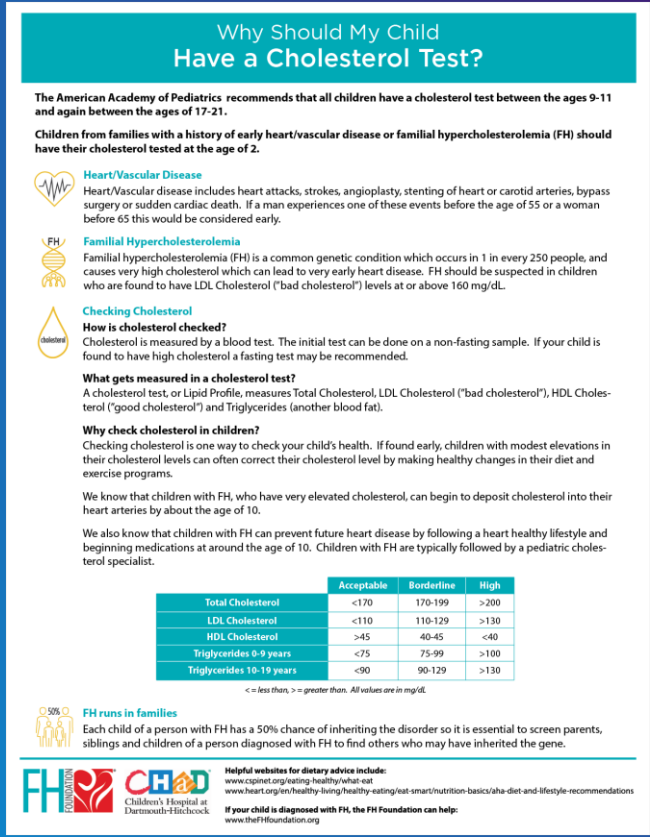
What about parents/children?

- Parents are not used to their children getting lab studies
- Parents don’t understand why their child should get a lipid profile
- Children don’t like getting their blood drawn ….. *But parents make lots of decisions children don’t like … think immunizations!*

What needs to happen?

- Physician Education and understanding of both the guidelines and familial hypercholesterolemia
- Local Lipid Champion (lipid specialist or pediatric cardiology)
- Improved understanding of statins / ezetimibe

Educate parents: pediatric poster



Why Should My Child Have a Cholesterol Test?

The American Academy of Pediatrics recommends that all children have a cholesterol test between the ages 9-11 and again between the ages of 17-21.

Children from families with a history of early heart/vascular disease or familial hypercholesterolemia (FH) should have their cholesterol tested at the age of 2.

Heart/Vascular Disease

Heart/Vascular disease includes heart attacks, strokes, angioplasty, stenting of heart or carotid arteries, bypass surgery or sudden cardiac death. If a man experiences one of these events before the age of 55 or a woman before 65 this would be considered early.

Familial Hypercholesterolemia

Familial hypercholesterolemia (FH) is a common genetic condition which occurs in 1 in every 250 people, and causes very high cholesterol which can lead to very early heart disease. FH should be suspected in children who are found to have LDL Cholesterol ("bad cholesterol") levels at or above 160 mg/dL.

Checking Cholesterol

How is cholesterol checked?

Cholesterol is measured by a blood test. The initial test can be done on a non-fasting sample. If your child is found to have high cholesterol a fasting test may be recommended.

What gets measured in a cholesterol test?

A cholesterol test, or Lipid Profile, measures Total Cholesterol, LDL Cholesterol ("bad cholesterol"), HDL Cholesterol ("good cholesterol") and Triglycerides (another blood fat).

Why check cholesterol in children?

Checking cholesterol is one way to check your child's health. If found early, children with modest elevations in their cholesterol levels can often correct their cholesterol level by making healthy changes in their diet and exercise programs.

We know that children with FH, who have very elevated cholesterol, can begin to deposit cholesterol into their heart arteries by about the age of 10.

We also know that children with FH can prevent future heart disease by following a heart healthy lifestyle and beginning medications at around the age of 10. Children with FH are typically followed by a pediatric cholesterol specialist.

	Acceptable	Borderline	High
Total Cholesterol	<170	170-199	>200
LDL Cholesterol	<110	110-129	>130
HDL Cholesterol	>45	40-45	<40
Triglycerides 0-9 years	<75	75-99	>100
Triglycerides 10-19 years	<90	90-129	>130

< = less than, > = greater than. All values are in mg/dL

FH runs in families

Each child of a person with FH has a 50% chance of inheriting the disorder so it is essential to screen parents, siblings and children of a person diagnosed with FH to find others who may have inherited the gene.

FH Foundation

CHaD Children's Hospital at Dartmouth-Hitchcock

Helpful websites for dietary advice include:
www.cspinet.org/eating-healthy/what-eat
www.heart.org/en/healthy-living/healthy-eating/eat-smart/nutrition-basics/aha-diet-and-lifestyle-recommendations

If your child is diagnosed with FH, the FH Foundation can help:
www.theFHfoundation.org

Make it easy!!!

- Pre-populate the 10-year-old visit with non-fasting lipid panel

- Facilitate with POC Screening – no lab visit required
  - Cholestech LDX™ – screening desktop analyzers
  - Barrier to this is lack of interface with EHR

- Public awareness campaign in NH

Jane B

- When I met Jane, her daughters were 21 and 23 and had never been screened

- Both of them have FH

FH impacts families

- Jane is now 73

- 4 of her 8 grandchildren have been diagnosed with FH and are treated with statins

FH impacts families

Lisa Khalafi

- Lisa is the daughter, granddaughter and great-granddaughter of women with FH. Jane is her mother. Four of Jane's eight grandchildren have FH.

- Lisa herself has FH. She is a tireless FH Advocate and special educator who has generously agreed to join me today to tell her FH Story.