Lipids and Genetics

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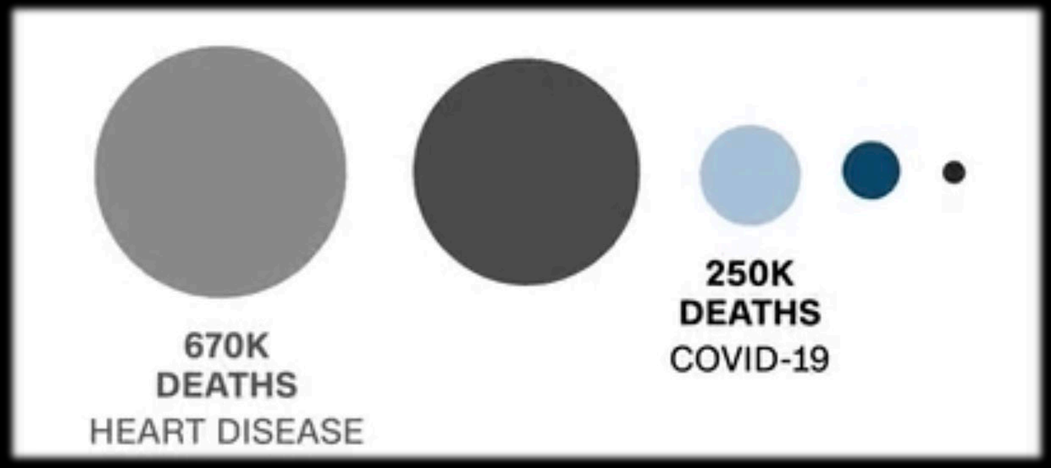
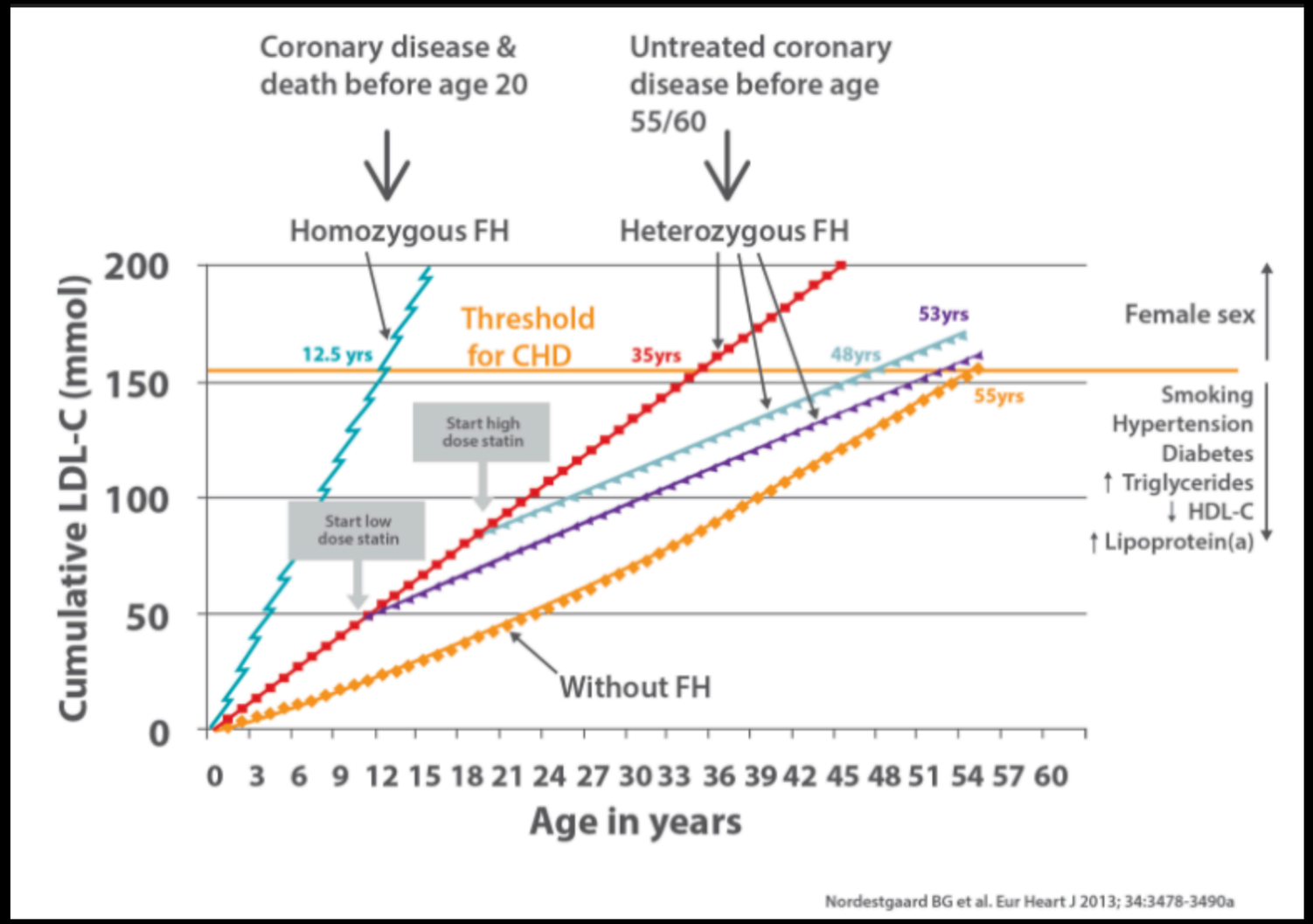


What is Familial Hyperlidemia

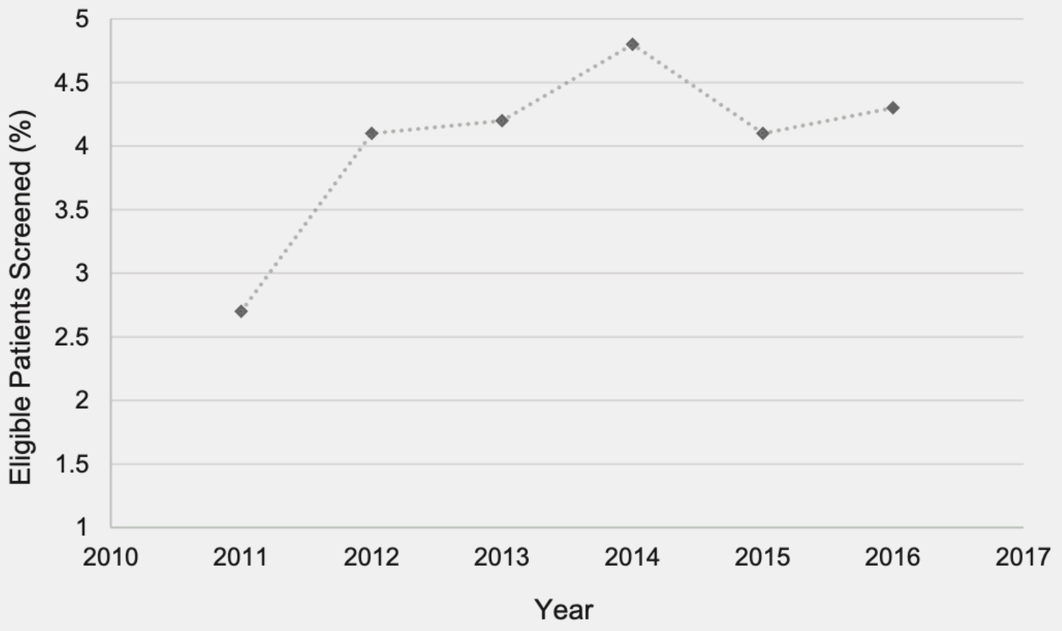
Why



1. Among individuals with LDL-C >190 mg/dL

- Gene positive = 22 fold increase risk of CVD compared to those with no gene positive and normal lipids
- Gene negative is a 6 fold increase compared to those with normal lipids

Pediatric cholesterol screening practices in 9- to 11-year-olds in a large midwestern primary care setting



Year	2011	2012	2013	2014	2015	2016
Screened Children, n (N=1995)	276	366	379	357	295	322
Total Children, n (N=50302)	10336	8906	8939	7418	7188	7515
Screening Rate, %	2.7	4.1	4.2	4.8	4.1	4.3

2019-2020 Compliance with Universal Lipid Screening Sanford, Fargo ND

- Well Child 9-11 years of age: 3772
- Lipid tests ordered: 707
- % compliance: 12-19%

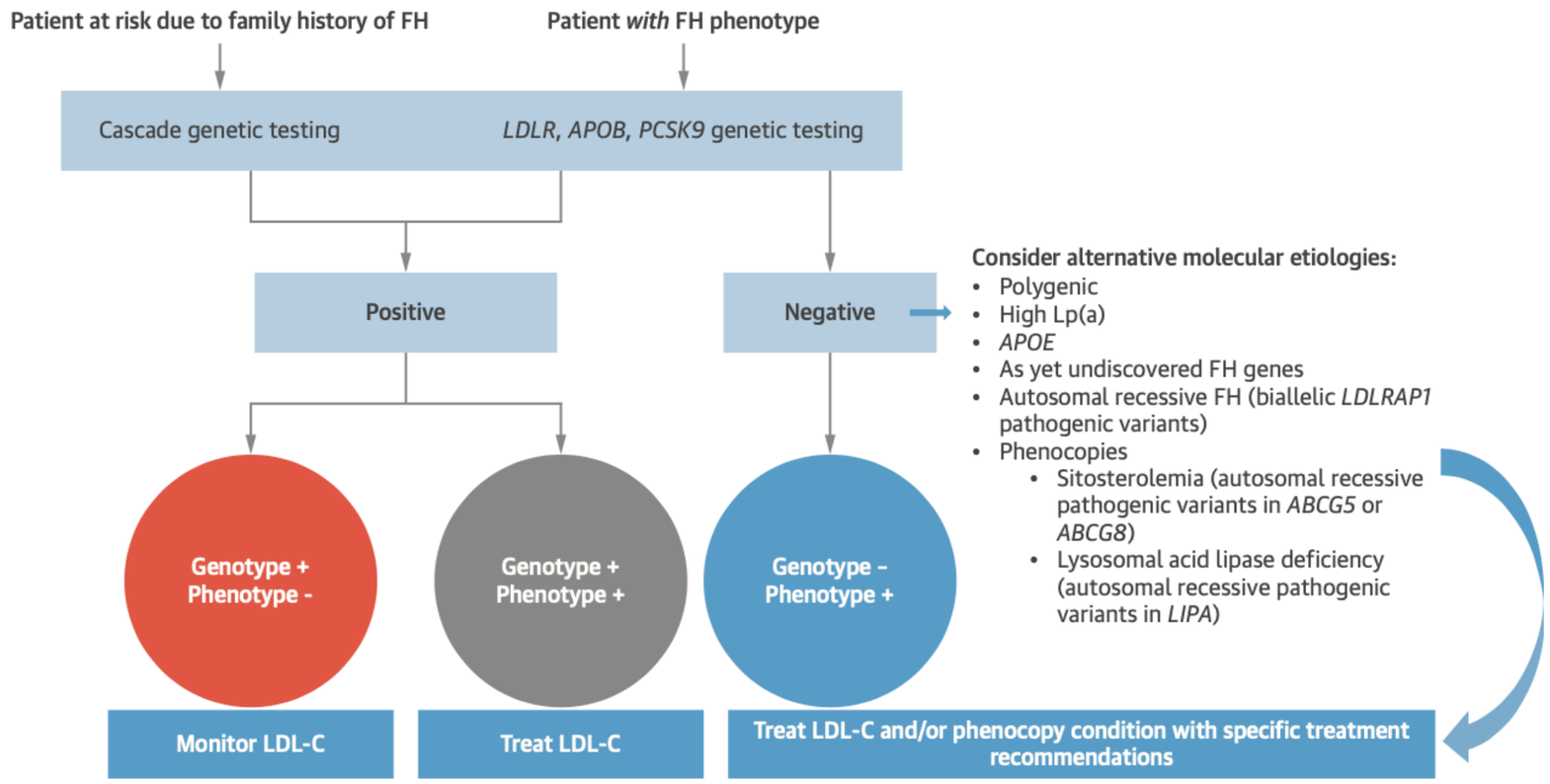
N	O	P	Q	R	S	T	U	V	W	X	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH
US(MED) Crie	Genetic	Genetic	VUS	Mutation	LP1 Date	LDI	CH	TG1	HLD	NON	ALT	CPK	Intervention	Date of T	Treatment	Dose 1	Side	LP2 Dat	LDI	CH
Yes	Invitae FH	LDLR		c.301G>A (p.Glu10	12/4/2019	340	426	138	58	368	18	117	Statin therapy	12/4/19	Atorvastatin	5 mg	None	1/4/20	211	290
Yes	Invitae FH	LDLR		c.301G>A (p.Glu10	12/4/2019	271	361	232	44	317	25	111	Statin therapy	12/4/19	Atorvastatin	10 mg	None	1/4/20	164	248
Yes	in process				12/17/2019	269	343	72	60	283			Clinic Follow in 6 months		Rosuvastatin	10 mg	None	7/28/20	163	237
Yes	Invitae FH	LDLR		c.301G>A (p.Glu10	12/4/2019	215	335	215	37	298	16	72	Statin therapy	12/4/19	Atorvastatin	10 mg	None	1/4/20	167	225
Yes					11/5/2019	233	331	142	70	261										
Yes	Invitae FH	LDLR			2/20/2019	259	325	100	46	279	6	71	Statin therapy	2/20/19	Pravastain	40 mg	None			
Yes	Invitae FH	LDLR		c.974G>A (p.cys32	10/7/2019	214	308	55	83	225			Statin therapy	12/10/19	Rosuvastatin	10 mg	None	3/4/20	108	194
Yes	MLOS				12/30/2019	219	297	84	61	236	27	90	Statin therapy	1/3/20	Atorvastatin	20 mg	None	3/20/20	165	235
Yes					11/5/2019	198	297	292	41	256			Clinic Follow in 6 months					3/2/20	202	297
Yes					3/4/2020	182	296	309	52	244	36		Lifestyle changes							
Yes	Invitae FH	LDLR		Partial deletions E	11/25/2019	217	284	130	41	243	21		Statin therapy	2/7/20	Simvastatin	10 mg	None	3/10/20	200	276
Yes					12/6/2019		275	527	57	218	59	82	Statin therapy		Atorvastatin	10 mg	None	3/2/20		240
Yes	Invitae FH	LDLR		heterozygous c.14	10/18/2018	213	268	72	41	227	9	94	Lifestyle changes	12/18/19	atorvastatin	10 mg	None	3/11/20	105	155
No	Referral made				6/2/2020	161	265	178	68	197	22		Clinic Follow in 6 months							
Yes	Invitae FH	LDLR		Partial deletion Ex	11/25/2019	211	264	100	33	231			Statin therapy	2/7/20	Simvastatin	10 mg	None	3/10/20	234	308
No	MLOS				2/10/2020	166	264	224	45	219	54							6/3/20	132	214
Yes	in process				3/16/2020	192	261	128	43	218	16		Statin therapy	3/26/20	Simvastatin	20 mg	Musculo	9/1/20		
Yes					8/28/2019	154	244	238	42	202			Lifestyle changes					9/5/19	132	206
Yes					10/18/2019	142	240	103	77	163			Lifestyle changes					12/24/19	134	235
					8/16/2019		233	445	32	201	41									
No					6/2/2020	151	232	171	47	185	27		Clinic Follow in 6 months							
Yes	in process				5/20/2020	181	231	95	31	200	15		Clinic Follow in 6 months							
No	Invitae FH	LDLR			3/20/2019	156	216	102	40	176										
No					2/14/2020	155	212	120	33	179			Follow up with PCP							
No	Gene DX e	APO A-5			12/27/2019		211	901	21	190	17							5/29/20		211
No	Referral made				6/10/2020	149	211	70	48	163			Clinic Follow in 6 months							
No	MLOS				12/31/2019	133	209	142	48	161			Lifestyle changes					3/2/20	94	147
No					8/28/2019	133	207	51	64	143			Lifestyle changes					1/27/20	145	221
No					2/27/2020	145	205	70	46	159	21	164	Lifestyle changes	6/1/20				6/4/20	166	240
No					6/11/2019	103	203	321	36	167	28	152	Lifestyle changes							
No					2/12/2020	126	202	153	45	157								9/1/20	128	195
No					10/17/2019	120	199	199	39	160			Lifestyle changes							
No					6/17/2019	109	195	228	40	155			Lifestyle changes							
No	N/A				8/5/2019		186	464	52	134			Lifestyle changes					11/27/19	84	159
No	MLOS				3/2/2020	124	185	102	41	144	29		Lifestyle changes					8/26/20	168	259
No	MLOS				12/31/2019	101	164	170	29	135	13		Lifestyle changes							

Role of Genetics

2018 JACC statement

Clinical Genetic Testing for Familial Hypercholesterolemia JACC Scientific Expert Panel

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.

2018 JACC statement

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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

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

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

If LDL-C values are unavailable, total cholesterol values ≥320, 260, and 230 mg/dl (corresponding to LDL-C levels ≥250, 190, and 160 mg/dl, respectively) could be used. *Two or more measurements, including assessment after intensive lifestyle modification. †Hypothyroidism, diabetes, renal disease, nephrotic syndrome, liver disease, medications. ‡Premature coronary artery disease (CAD) = male subjects ≤55 years of age, female subjects ≤65 years of age; adapted from the American Heart Association phenotype definition of HeFH. Other abbreviations as in Table 1.

2018 JACC statement

Clinical Genetic Testing for Familial Hypercholesterolemia JACC Scientific Expert Panel

- The Expert Panel panel recommends that genetic testing become the **Standard Of Care** for patients with definitive or probable FH, as well as for the at risk relatives

2020
Scientific Statement

Scientific Statement

Genetic testing in dyslipidemia: A scientific statement from the National Lipid Association

Check for updates

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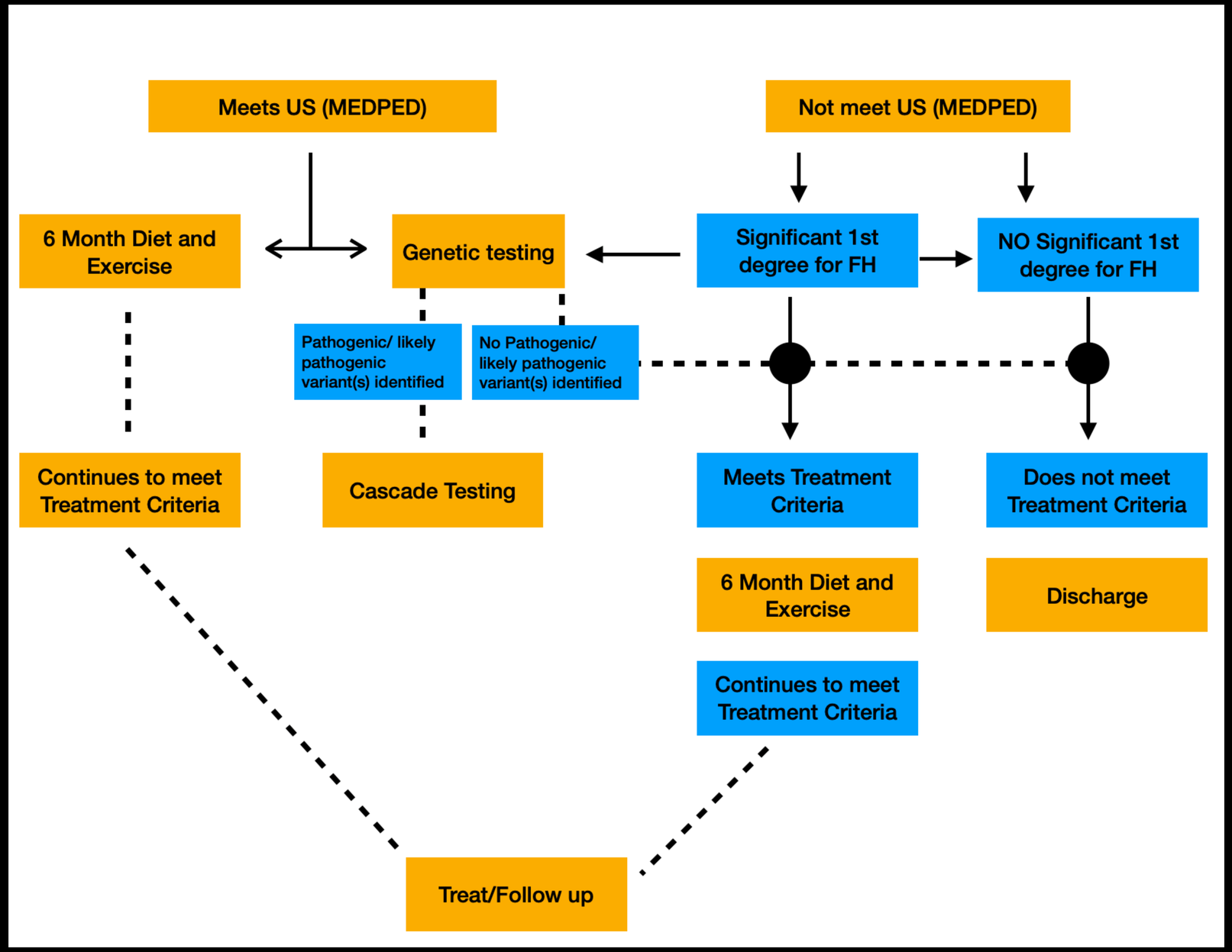
Meets US (MEDPED)
Not meet US (MEDPED)
6 Month Diet and Exercise
Genetic testing
Significant 1st degree for FH
NO Significant 1st degree for FH
Pathogenic/ likely pathogenic variant(s) identified
No Pathogenic/ likely pathogenic variant(s) identified
Continues to meet Treatment Criteria
Cascade Testing
Meets Treatment Criteria
Does not meet Treatment Criteria
6 Month Diet and Exercise
Discharge
Continues to meet Treatment Criteria
Treat/Follow up

Advocacy

- 1. We would like to improve compliance of universal screening for lipids both throughout Sanford and state wide
  - AAP winter Conference
  - We are holding a lunch and learn in December as part of a continuous effort to help inform
  - We are currently expanding to Sioux Falls and developing a second lipidology team
- We would like to increase accessibility of genetics within this population