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Familial Hypercholesterolemia

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Abstract

Familial hypercholesterolemia is a genetic and metabolic disorder associated with an increased risk of morbidity and mortality. Two main types of familial hypercholesterolemia are distinguished: heterozygous familial hypercholesterolemia and homozygous familial hypercholesterolemia. Homozygous familial hypercholesterolemia progresses much more aggressively with higher levels of LDL-C and higher risk of cardiovascular disease at earlier ages. The prognosis of homozygous familial hypercholesterolemia largely depends on the LDL-C levels. Reducing the LDL-C level is one of the primary goals of treatment patients with familial hypercholesterolemia. Effective control of LDL-C significantly reduces the cardiovascular morbidity and mortality. Understanding the factors likely to affect treatment adherence is paramount. Adherence to treatment can be improve when a genetic etiology is confirmed. Positive genetic test result has beneficial effects on adherence to pharmacotherapy and in achieving LDL-C levels reduction.

Keywords: familial hypercholesterolemia, adherence, illness perception, barriers, diagnose

1. Introduction

This chapter reviews the definition, etiology, course and treatment of familial hypercholesterolemia, and analyses the influence of some factors that may influence the early diagnosis of familial hypercholesterolemia and the treatment of familial hypercholesterolemia.

2. Definition and etiology of familial hypercholesterolemia

Familial hypercholesterolemia (FH) is a genetic and metabolic disorder that affects the metabolism of cholesterol [1–10].

Currently, the genes involved in HF are the following: low-density lipoprotein receptor (LDLR) gene, apolipoprotein B-100 (APOB) gene and proprotein convertase subtilisin kexin type 9 (PCSK9) gene, LDLR adaptor protein 1 (LDLRAP1) gene [1–10]. See **Table 1**.

The mutation in LDLR gene, APOB gene and PCSK9 gene is inherited following an autosomal dominant/autosomal co-dominant pattern and the mutation in LDLRAP1 gene is inherited following an autosomal recessive pattern [1–10].

Mutations of the genes cause defective LDL uptake and degradation, which in-turn leads to an elevation of plasma low-density lipoprotein-cholesterol (LDL-C) level, producing the hypercholesterolemia phenotype. The chronic exposure to high levels of LDL-C lead to the development of atherosclerosis and cardiovascular disease at an early age [1–10].

Gene	Protein	Chromosomal location	Proportion of patients with FH
LDLR	LDL receptor	19p13.2	80–85%
APOB	Apolipoprotein B100	2p24.1	5–10%
PCSK9	Proprotein convertase subtilisin kexin type 9	1p32.3	< 1%
LDLRAP1	LDL receptor adaptor protein 1	1p36.11	< 1%

Table 1.
Genes involved in familial hypercholesterolemia.

Two main types of HF are distinguished: heterozygous familial hypercholesterolemia and homozygous familial hypercholesterolemia. Heterozygous familial hypercholesterolemia is usually caused by a single pathogenic variant in one of the genes associated with familial hypercholesterolemia, mostly in LDLR. Homozygous familial hypercholesterolemia is caused by biallelic pathogenic variants, generally in LDLR [1–10].

3. Diagnosis of familial hypercholesterolemia

Familial hypercholesterolemia often diagnosed using the following diagnostic criteria: UK Simon Broome System and the Dutch Lipid Clinic Network criteria [11–17]. The UK Simon Broome System Criteria can be applied in children/adolescents/adults. The items included in Simon Broome System are the following: laboratory findings (total cholesterol or LDL-C), physical examination (tendon xanthomas), molecular diagnosis (mutation LDLR, APOB or PCSK9), and family history (myocardial infarction, raised total cholesterol) [11–17]. UK Simon Broome System Criteria is attached in **Table 2**.

Items	Criterion
In adults (age ≥ 16): total cholesterol level > 290 mg/dL or LDL-C > 190 mg/dL	A
In children (age < 16): total cholesterol level > 260 mg/dL or LDL-C > 155 mg/dL	B
Tendon xanthomas in the patient or in a first- or second-degree relative	
DNA-based evidence of a mutation in LDLR, APOB, or PCSK9	C
Family history of myocardial infarction before age 50 in a second-degree relative, or before age 60 in a first degree relative	D
Total cholesterol >290 mg/dL in a first- or second degree relative	E
C or A plus B: Definite familial hypercholesterolemia	
A plus D or A plus E: Probable familial hypercholesterolemia	

Table 2.
UK Simon Broome system criteria.

The Dutch Lipid Clinic Network Criteria can be applied in adults. The items included in Dutch Lipid Clinic Network are the following: laboratory findings (LDL- C), physical examination (tendon xanthomas, arcus cornealis), molecular diagnosis (mutation LDLR, APOB or PCSK9), family history (atherosclerotic cardiovascular disease, tendon xanthomas, arcus cornealis, raised LDL- C), and patient history (coronary artery disease, cerebral or peripheral vascular disease) [11–17]. Dutch Lipid Clinic Network Criteria is attached in **Table 3**.

The diagnostic criteria mentioned differ in the items included and, in the items necessary to make a definitive FH diagnosis. In the Simon Broome criteria, a positive genetic test is sufficient for a definitive diagnosis of familial hypercholesterolemia. In the Dutch Lipid Clinic Network criteria, a positive genetic test should be accompanied by an additional item (for example, elevated LDL-C levels) to fulfill the definite diagnosis criteria [11–17].

Although all the criteria mentioned include LDL- C levels, there are variations in the cut-offs necessary for the diagnosis of familial hypercholesterolemia. It is worth mentioning that untreated LDL-C levels vary across genotypes. For example: levels are highest with two LDLR null alleles, lower with two LDLR defective alleles or two mutant PCSK9 alleles, and lowest with two mutant APOB alleles and in double heterozygotes [18–26].

Regardless of the diagnostic criterion used, before the diagnosis of familial hypercholesterolemia is confirmed, secondary causes of hypercholesterolemia should be excluded such as hypothyroidism, renal disease, nephrotic syndrome, liver disease and diets with extremely elevated saturated fat/cholesterol content.

Items	Score
First-degree relative with known premature atherosclerotic cardiovascular disease (age < 55 in men, age < 60 in women) or first-degree relative with LDL-C > 95th percentile	1
First-degree relative with tendon xanthomas or arcus cornealis, or child (under age 18) with LDL-C > 95th percentile	2
Premature coronary artery disease	2
Premature cerebral or peripheral vascular disease	1
Tendon xanthomas	6
Arcus cornealis before age 45	4
LDL-C ≥ 330 mg/dL	8
LDL-C between 250 and 329 mg/dL	5
LDL-C between 190 and 249 mg/dL	3
LDL-C between 155 and 189 mg/dL	1
Functional mutation in the LDLR, APOB, or PCSK9 gene	8
Score > 8 Definite familial hypercholesterolemia	
Score between 6 and 8 Probable familial hypercholesterolemia	
Score between 3 and 5 Possible familial hypercholesterolemia	
Score < 3 Unlikely	

Table 3.
Dutch lipid clinic network criteria.

Furthermore, there are several conditions with overlapping laboratory findings or family history features that might be considered when a diagnosis of familial hypercholesterolemia is suspected. For example: sitosterolaemia (xanthomas and hypercholesterolemia caused by an autosomal recessive pathogenic variant in *ABCG5* or *ABCG8*) and lysosomal acid lipase deficiency (elevated LDL-C levels accompanied by fatty liver disease could be caused by an autosomal recessive pathogenic variant in *LIPA*) [27–29].

Once an individual is identified with familial hypercholesterolemia (index case) the cascade screening of family members of the known index case is recommended for identifying new cases of familial hypercholesterolemia. Cascade screening could include LDL-C measurement, genetic testing, or both [11–17, 30].

Though the diagnosis of familial hypercholesterolemia can be performed without genetic testing (for example, using Simon Broome criteria), when a mutation compatible with familial hypercholesterolemia is identified, genetic testing serves to confirm the diagnosis of FH. Furthermore, genetic testing could provide discrimination, at the molecular genetic level, between homozygous familial hypercholesterolemia and heterozygous familial hypercholesterolemia. Moreover, pre-test and post-test genetic counseling can facilitate patient's interpretation of genetic test results [11–17].

The International Classification of Diseases, 10th Revision, has a specific diagnosis criteria for homozygous familial hypercholesterolemia and heterozygous familial hypercholesterolemia (E78.01) [31].

The ICD10 criteria for heterozygous familial hypercholesterolemia are the following: LDL-C ≥ 160 mg/dL (4 mmol/L) for children or LDL-C ≥ 190 mg/dL (5 mmol/L) for adults and: a first-degree relative who is similarly affected or a first-degree relative with positive genetic testing for an LDL cholesterol-raising defect in *LDLR*, *APOB* or *PCSK9* [31].

The ICD10 criteria for Homozygous familial hypercholesterolemia are the following: LDL-C ≥ 400 mg/dL (10 mmol/L) and: one or both parents with clinically diagnosed familial hypercholesterolemia or one or both parents with positive genetic testing for two identical (homozygous familial hypercholesterolemia) or non-identical (compound or double heterozygous familial hypercholesterolemia) LDL cholesterol-raising gene defects in *LDLR*, *APOB* or *PCSK9* or one or both parents with autosomal recessive familial hypercholesterolemia [31].

Familial hypercholesterolemia is considered underdiagnosed. During the diagnosis process, some barriers might arise to early diagnosis of familial hypercholesterolemia in patients and relatives. From medical point, for example: physician's knowledge of FH diagnoses and treatment, the lack of a uniform clinical criteria for FH diagnosis, the availability of genetic testing, physician's knowledge about screening methods (selective, opportunistic, universal, cascade) and the identification of probable cases in different health care levels. From patient point, for example: some patients do not want a personal diagnosis to be disclosed to relatives, some parents experience feelings of guilt related to passing their mutation to their children, and many patients interpret their negative genetic test result as meaning they do not have FH hypercholesterolemia or that their FH hypercholesterolemia is not genetic and thus their relatives cannot have FH [1, 32].

Machine learning and deep learning approach could enhance the identification of familial hypercholesterolemia patients using electronic health record data. For example: the FIND FH model. This model recognizes the clinical phenotype for familial hypercholesterolemia and provides the framework for a HIPAA-compliant method to contact these identified individuals with FH [33–36].

4. Course disease and treatment of familial hypercholesterolemia

The signs and symptoms of homozygous familial hypercholesterolemia and heterozygous familial hypercholesterolemia are similar. However, homozygous FH patients have higher levels of LDL-C and higher risk of cardiovascular disease. The disease progresses much more aggressively, the phenotype become clinical manifest earlier, and cardiovascular events occur at earlier ages in homozygous FH patients. Cardiovascular risk factors and lipoprotein(a) levels adversely affect the course of homozygous and heterozygous FH diseases increasing coronary heart disease rates [11–12, 14–16, 37–43].

The prognosis of homozygous familial hypercholesterolemia and heterozygous familial hypercholesterolemia largely depends on the LDL-C levels. Reducing the LDL-C level is one of the primary goals of treatment homozygous and heterozygous FH. Effective control of LDL-C significantly reduces the cardiovascular morbidity and mortality. To improve cardiovascular risk assessment, the use of imaging techniques to detect asymptomatic atherosclerosis is recommended in both homozygous and heterozygous FH [11–12, 14–16, 41–43].

The carotid intima-media thickness is greater and aortic lesions can be seen identified in heterozygous FH patients between 8 to 10 years of age. During adolescence about 25% of the adolescents with heterozygous FH have demonstrable coronary artery calcium. Clinical manifestation of coronary heart disease can be evident in heterozygous FH patients during the third decade of life. Physical manifestations of sustained elevations of LDL-C (tendon xanthomas and corneal arcus) become apparent during adulthood [44–49].

At birth, homozygous familial hypercholesterolemia patients have a ≥ 4 -fold increase in plasma LDL-C concentrations. Since early in life cholesterol deposits in tendons (xanthomas), in the cornea (corneal arcus) and around the eye (xanthelasma). Furthermore, cholesterol deposits in coronary arteries, carotid arteries, aortic root, and valve. Therefore, coronary heart disease and supraaortic and aortic valve stenosis are possible causes of death. Young adults with homozygous familial hypercholesterolemia often require aortic valve replacement. Non-invasive imaging can be used to monitor atherosclerotic and aortic valve disease progression in homozygous FH patients and to adjusted treatment [50–55].

Treatment of FH is long-term and involves pharmacotherapy, lifestyle modifications and control other cardiovascular risk factors such as hypertension, diabetes, tobacco smoking, obesity, and sedentary behavior [12, 14–16, 41–42, 56–61].

Statins are the mainstay pharmacotherapy. However, if maximal tolerated dose of statin is used and LDL-C goal not achieved, statins usually combined with ezetimibe. Additionally, if using statin-ezetimibe combination LDL-C goal not achieved, adding PCSK9 inhibitors is considered [12, 14–16, 41–42, 56–65]. The European Atherosclerosis Society/European Society of Cardiology plasma low-density lipoprotein-cholesterol goals [57] for patients with familial hypercholesterolemia are summarized in **Table 4**.

Patients with PCSK9 mutations are particularly responsive to PCSK9 inhibition. However, PCSK9 inhibitors had no effect on LDL cholesterol in those with two LDLR null alleles with homozygous familial hypercholesterolemia. Moreover, if at least one allele had residual LDLR activity, PCSK9 inhibitors lowered LDL cholesterol in patients with homozygous familial hypercholesterolemia [66–69].

Incomplete/low adherence to treatment is associated with increased risk of cardiovascular disease. A proportion of FH patients fall short of full compliance or follow regimens inconsistently. Understanding the factors likely to affect treatment adherence is paramount [70–79].

The European Atherosclerosis Society/European Society of Cardiology (2019) recommends the following goals for plasma low-density lipoprotein-cholesterol for patients with familial hypercholesterolemia:
LDL-C < 3.5 mmol/L in children
LDL-C < 1.8 mmol/L and a reduction in plasma LDL-C of >50% in subjects without other major risk factors (high risk)
LDL <1.4 mmol/L and a reduction in plasma LDL-C > 50% in subjects with one or more major cardiovascular disease (CVD) risk factors and/or existing CVD (very high risk)

Table 4.
LDL-C goals for patients with familial hypercholesterolemia.

As well as in other chronic pathologies that require long-term treatment, psychological and cognitive issues can influence adherence to treatment [70–79].

While there is no evidence of depression or anxiety in FH patients, instead there is evidence of cognitive deficits and mild cognitive impairment in FH patients. Deficits in executive functioning and memory may affect medication adherence because taking medicines involves developing and implementing a plan to adhere and remembering the plan (for example: the plan may require time-based (e.g., at 8:00 p.m.) or event-based prospective remembering (e.g., with meals) and remembering what medicine take and whether the medicine was taken). Furthermore, executive functions may affect the achievement of lifestyle modifications and maintain healthy behavior over time included in FH management [70–76].

Illness perceptions may affect adherence to both lifestyle interventions and medications. Perception of illness/perception of risk may affect FH patient behavior. Risk perception may be changed by personal or familiar events, such as a cardiovascular event in the family, a change in or an onset of symptoms and becoming parent. Health staff need to recognize variation in patient’s risk perception because it can affect medical treatment [77–79].

Adherence to FH treatment can be improve when a genetic etiology is confirmed. Positive genetic test result has beneficial effects on adherence to pharmacotherapy and in achieving LDL-C levels reduction. Patients whose diagnosis was confirmed by genetic testing perceived diagnosis more accurate, believed more strongly that genes controlled their cholesterol and have higher perceived efficacy of medication. In children with FH, parents are critical in promoting treatment adherence [77, 80–85].

5. Conclusions

Although the diagnosis of familial hypercholesterolemia can be performed without genetic testing, knowledge about the genetic status of an individual with familial hypercholesterolemia can improve understand of risk and prognosis as well as improve managing familial hypercholesterolemia. Adherence to FH treatment can be improve when a genetic etiology is confirmed.

Conflict of interest

The authors declare no conflict of interest.

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References

- [1] Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease. *Eur Heart J* 2013;34:3478-90a.
- [2] Kastelein JJP, Reeskamp LF, Hovingh GK. Familial Hypercholesterolemia: The Most Common Monogenic Disorder in Humans. *J Am Coll Cardiol*. 2020;75(20):2567-2569. doi: 10.1016/j.jacc.2020.03.058.
- [3] Bianconi V, Banach M, Pirro M; International Lipid Expert Panel (ILEP). Why patients with familial hypercholesterolemia are at high cardiovascular risk? Beyond LDL-C levels. *Trends Cardiovasc Med*. 2020:S1050-1738(20)30041-4. doi: 10.1016/j.tcm.2020.03.004.
- [4] Brandts J, Dharmayat KI, Ray KK, Vallejo-Vaz AJ. Familial hypercholesterolemia: is it time to separate monogenic from polygenic familial hypercholesterolemia? *Curr Opin Lipidol*. 2020;31:111-118.
- [5] Beheshti SO, Madsen CM, Varbo A, Nordestgaard BG. Worldwide Prevalence of Familial Hypercholesterolemia: Meta-Analyses of 11 Million Subjects. *J Am Coll Cardiol*. 2020;75(20):2553-2566. doi: 10.1016/j.jacc.2020.03.057.
- [6] Representatives of the Global Familial Hypercholesterolemia Community, Wilemon KA, Patel J, Aguilar-Salinas C, Ahmed CD, Alkhneifawi M, Almahmeed W, Alonso R, Al-Rasadi K, Badimon L, Bernal LM, Bogsrud MP, Braun LT, Brunham L, Catapano AL, Cillíková K, Corral P, Cuevas R, Defesche JC, Descamps OS, de Ferranti S, Eiselé JL, Elikir G, Folco E, Freiburger T, Fuggetta F, Gaspar IM, Gesztes ÁG, Grošelj U, Hamilton-Craig I, Hanauer-Mader G, Harada-Shiba M, Hastings G, Hovingh GK, Izar MC, Jamison A, Karlsson GN, Kayikcioglu M, Koob S, Koseki M, Lane S, Lima-Martinez MM, López G, Martinez TL, Marais D, Marion L, Mata P, Maurina I, Maxwell D, Mehta R, Mensah GA, Miserez AR, Neely D, Nicholls SJ, Nohara A, Nordestgaard BG, Ose L, Pallidis A, Pang J, Payne J, Peterson AL, Popescu MP, Puri R, Ray KK, Reda A, Sampietro T, Santos RD, Schalkers I, Schreier L, Shapiro MD, Sijbrands E, Soffer D, Stefanutti C, Stoll M, Sy RG, Tamayo ML, Tilney MK, Tokgözoğlu L, Tomlinson B, Vallejo-Vaz AJ, Vazquez-Cárdenas A, de Luca PV, Wald DS, Watts GF, Wenger NK, Wolf M, Wood D, Zegerius A, Gaziano TA, Gidding SS. Reducing the Clinical and Public Health Burden of Familial Hypercholesterolemia: A Global Call to Action. *JAMA Cardiol*. 2020;5(2):217-229. doi: 10.1001/jamacardio.2019.5173.
- [7] Defesche JC, Gidding SS, Harada-Shiba M, Hegele RA, Santos RD, Wierzbicki AS. Familial hypercholesterolaemia. *Nat Rev Dis Primers*. 2017;3:17093. doi: 10.1038/nrdp.2017.93.
- [8] Bouhairie VE, Goldberg AC. Familial hypercholesterolemia. *Cardiol Clin* 2015;33:169-179.
- [9] Singh S, Bittner V. Familial hypercholesterolemia--epidemiology, diagnosis, and screening. *Curr Atheroscler Rep* 2015;17:482.
- [10] Watts GF, Lewis B, Sullivan DR. Familial hypercholesterolemia: a missed opportunity in preventive medicine. *Nat Clin Pract Cardiovasc Med* 2007;4:404-405.
- [11] Turgeon RD, Barry AR, Pearson GJ. Familial hypercholesterolemia: Review

of diagnosis, screening, and treatment. *Can Fam Physician*. 2016;62(1):32-37.

[12] McGowan MP, Hosseini Dehkordi SH, Moriarty PM, Duell PB. Diagnosis and Treatment of Heterozygous Familial Hypercholesterolemia. *J Am Heart Assoc*. 2019;8(24):e013225. doi:10.1161/JAHA.119.013225

[13] Shah NP, Ahmed HM, Wilson Tang WH. Familial hypercholesterolemia: detect, treat, and ask about family. *Cleve Clin J Med* 2020;87:109-120.

[14] Pang J, Sullivan DR, Brett T, Kostner KM, Hare DL, Watts GF. Familial hypercholesterolaemia in 2020: a leading Tier 1 genomic application. *Heart, Lung and Circulation*. 2020; 29(4), 619-633.

[15] Schmidt EB, Hedegaard BS, Retterstøl K. Familial hypercholesterolaemia: history, diagnosis, screening, management and challenges. *Heart*. 2020;106(24):1940-1946. doi: 10.1136/heartjnl-2019-316276.

[16] Alonso R, Perez de Isla L, Muniz-Grijalvo O; Diaz-Diaz JL, Mata P. Familial hypercholesterolaemia diagnosis and management. *Eur Cardiol* 2018;13:14-20.

[17] Defesche JC, Gidding SS, Harada-Shiba M, Hegele RA, Santos RD, Wierzbicki AS. Familial hypercholesterolaemia. *Nature reviews Disease primers*. 2017;3(1):1-20.

[18] Alves AC, Etxebarria A, Medeiros AM, Benito-Vicente A, Thedrez A, Passard M, Croyal M, Martin C, Lambert G, Bourbon M. Characterization of the first PCSK9 gain of function homozygote. *J Am Coll Cardiol*. 2015;66(19):2152-2154. doi: 10.1016/j.jacc.2015.08.871.

[19] Hopkins PN, Lane SR. Genotype-guided diagnosis in

familial hypercholesterolemia: clinical management and concerns. *Curr Opin Lipidol*. 2017;28(2):144-151. doi: 10.1097/MOL.0000000000000397.

[20] Bourbon M, Alves AC, Alonso R, Mata N, Aguiar P, Padró T, Mata P. Mutational analysis and genotype-phenotype relation in familial hypercholesterolemia: The SAFEHEART registry. *Atherosclerosis*. 2017;262:8-13. doi: 10.1016/j.atherosclerosis.2017.04.002.

[21] Wang J, Ban MR, Hegele RA. Multiplex ligation-dependent probe amplification of LDLR enhances molecular diagnosis of familial hypercholesterolemia. *J Lipid Res*. 2005;46(2):366-372. doi: 10.1194/jlr.D400030-JLR200.

[22] Berberich AJ, Hegele RA. The complex molecular genetics of familial hypercholesterolaemia. *Nat Rev Cardiol*. 2019;16(1):9-20. doi: 10.1038/s41569-018-0052-6.

[23] Santos RD, Gidding SS, Hegele RA, Cuchel MA, Barter PJ, Watts GF, Baum SJ, Catapano AL, Chapman MJ, Defesche JC, Folco E, Freiburger T, Genest J, Hovingh GK, Harada-Shiba M, Humphries SE, Jackson AS, Mata P, Moriarty PM, Raal FJ, Al-Rasadi K, Ray KK, Reiner Z, Sijbrands EJ, Yamashita S; International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel. Defining severe familial hypercholesterolaemia and the implications for clinical management: a consensus statement from the International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel. *Lancet Diabetes Endocrinol*. 2016;4(10):850-861. doi: 10.1016/S2213-8587(16)30041-9.

[24] Cuchel M, Bruckert E, Ginsberg HN, et al. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians

to improve detection and clinical management—a position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. *Eur Heart J* 2014; 35: 2146-2157.

[25] Kolansky DM, Cuchel M, Clark BJ, et al. Longitudinal evaluation and assessment of cardiovascular disease in patients with homozygous familial hypercholesterolemia. *Am J Cardiol* 2008;102: 1438-43.

[26] Moorjani S, Roy M, Torres A, et al. Mutations of low-density-lipoprotein-receptor gene, variation in plasma cholesterol, and expression of coronary heart disease in homozygous familial hypercholesterolaemia. *Lancet* 1993; 341: 1303-1306.

[27] Stitzel NO, Fouchier SW, Sjouke B, Peloso GM, Moscoso AM, Auer PL, Goel A, Gigante B, Barnes TA, Melander O, Orho-Melander M, Duga S, Sivapalaratnam S, Nikpay M, Martinelli N, Girelli D, Jackson RD, Kooperberg C, Lange LA, Ardissino D, McPherson R, Farrall M, Watkins H, Reilly MP, Rader DJ, de Faire U, Schunkert H, Erdmann J, Samani NJ, Charnas L, Altshuler D, Gabriel S, Kastelein JJ, Defesche JC, Nederveen AJ, Kathiresan S, Hovingh GK; National Heart, Lung, and Blood Institute GO Exome Sequencing Project. Exome sequencing and directed clinical phenotyping diagnose cholesterol ester storage disease presenting as autosomal recessive hypercholesterolemia. *Arterioscler Thromb Vasc Biol*. 2013;33(12):2909-14. doi: 10.1161/ATVBAHA.113.302426.

[28] Chora JR, Alves AC, Medeiros AM, Mariano C, Lobarinhas G, Guerra A, Mansilha H, Cortez-Pinto H, Bourbon M. Lysosomal acid lipase deficiency: A hidden disease among cohorts of familial hypercholesterolemia? *J Clin Lipidol*. 2017;11(2):477-484.e2. doi: 10.1016/j.jacl.2016.11.002.

[29] Berge KE, Tian H, Graf GA, Yu L, Grishin NV, Schultz J, Kwiterovich P, Shan B, Barnes R, Hobbs HH. Accumulation of dietary cholesterol in sitosterolemia caused by mutations in adjacent ABC transporters. *Science*. 2000;290(5497):1771-1775. doi: 10.1126/science.290.5497.1771.

[30] National Institute for Health and Care Excellence (NICE) Identification and management of familial hypercholesterolaemia. London: NICE; 2017. NICE clinical guideline CG71. <https://www.nice.org.uk/guidance/cg71> (accessed 2 January 2020)

[31] ICD List. ICD-10 Diagnosis Code E78.01: Familial hypercholesterolemia. ICD List <http://icdlist.com/icd-10/E78.01> (2017).

[32] Alonso R, Perez de Isla L, Muñoz-Grijalvo O, Mata P. Barriers to Early Diagnosis and Treatment of Familial Hypercholesterolemia: Current Perspectives on Improving Patient Care. *Vasc Health Risk Manag*. 2020;16:11-25. doi:10.2147/VHRM.S192401

[33] Ibrahim S, Reeskamp LF, Stroes ESG, Watts GF. Advances, gaps and opportunities in the detection of familial hypercholesterolemia: overview of current and future screening and detection methods. *Curr Opin Lipidol*. 2020;31(6):347-355. doi: 10.1097/MOL.0000000000000714. PMID: 33027222.

[34] Akyea RK, Qureshi N, Kai J, Weng SF. Performance and clinical utility of supervised machine-learning approaches in detecting familial hypercholesterolaemia in primary care. *NPJ Digit Med*. 2020;3(1):142. doi: 10.1038/s41746-020-00349-5. PMID: 33299097.

[35] Myers KD, Knowles JW, Staszak D, Shapiro MD, Howard W, Yadava M, Zuzick D, Williamson L, Shah NH, Banda JM, Leader J, Cromwell WC,

- Trautman E, Murray MF, Baum SJ, Myers S, Gidding SS, Wilemon K, Rader DJ. Precision screening for familial hypercholesterolaemia: a machine learning study applied to electronic health encounter data. *Lancet Digit Health*. 2019;1(8):e393-e402. doi: 10.1016/S2589-7500(19)30150-5.
- [36] Banda JM, Sarraju A, Abbasi F, Parizo J, Pariani M, Ison H, Briskin E, Wand H, Dubois S, Jung K, Myers SA, Rader DJ, Leader JB, Murray MF, Myers KD, Wilemon K, Shah NH, Knowles JW. Finding missed cases of familial hypercholesterolemia in health systems using machine learning. *NPJ Digit Med*. 2019;2:23. doi: 10.1038/s41746-019-0101-5.
- [37] Miname MH, Santos RD. Reducing cardiovascular risk in patients with familial hypercholesterolemia: Risk prediction and lipid management. *Prog Cardiovasc Dis*. 2019;62(5):414-422. doi: 10.1016/j.pcad.2019.10.003.
- [38] Vuorio A, Watts GF, Schneider WJ, Tsimikas S, Kovanen PT. Familial hypercholesterolemia and elevated lipoprotein(a): double heritable risk and new therapeutic opportunities. *J Intern Med*. 2020;287(1):2-18. doi: 10.1111/joim.12981.
- [39] Bianconi V, Banach M, Pirro M; International Lipid Expert Panel (ILEP). Why patients with familial hypercholesterolemia are at high cardiovascular risk? Beyond LDL-C levels. *Trends Cardiovasc Med*. 2020:S1050-1738(20)30041-4. doi: 10.1016/j.tcm.2020.03.004.
- [40] Alonso R, Andres E, Mata N, Fuentes-Jiménez F, Badimón L, López-Miranda J, Padró T, Muñiz O, Díaz-Díaz JL, Mauri M, Ordovás JM, Mata P; SAFEHEART Investigators. Lipoprotein(a) levels in familial hypercholesterolemia: an important predictor of cardiovascular disease independent of the type of LDL receptor mutation. *J Am Coll Cardiol*. 2014;63(19):1982-9. doi: 10.1016/j.jacc.2014.01.063.
- [41] Goldberg AC, Hopkins PN, Toth PP, et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol*. 2011;5:S1-S8.
- [42] Raal FJ, Santos RD. Homozygous familial hypercholesterolemia: current perspectives on diagnosis and treatment. *Atherosclerosis*. 2012;223(2):262-268. doi: 10.1016/j.atherosclerosis.2012.02.019.
- [43] Gidding SS, Champagne MA, De Ferranti SD, et al. The agenda for familial hypercholesterolemia: a scientific statement from the American Heart Association. *Circulation*. 2015;132:2167-2192.
- [44] Sijbrands EJ, Westendorp RG, Defesche JC, de Meier PH, Smelt AH, Kastelein JJ. Mortality over two centuries in large pedigree with familial hypercholesterolaemia: family tree mortality study. *BMJ*. 2001;322:1019-1023.
- [45] Das S, Zhang S, Mitchell D, Gidding SS. Metabolic syndrome with early aortic atherosclerosis in a child. *J Cardiometab Syndr*. 2006;1:286-287.
- [46] Jansen AC, van Wissen S, Defesche JC, Kastelein JJ. Phenotypic variability in familial hypercholesterolaemia: an update. *Curr Opin Lipidol*. 2002;13:165-171.
- [47] Kusters DM, Hutten BA, McCrindle BW, Cassiman D, Francis GA, Gagne C, Gaudet D, Morrison KM, Langslet G, Kastelein JJ, Wiegman A. Design and baseline data of a pediatric study with rosuvastatin in familial hypercholesterolemia. *J Clin*

Lipidol. 2013;7:408-413. doi: 10.1016/j.jacl.2013.06.010.

[48] Umans-Eckenhausen MA, Sijbrands EJ, Kastelein JJ, Defesche JC. Lowdensity lipoprotein receptor gene mutations and cardiovascular risk in a large genetic cascade screening population. *Circulation*. 2002;106:3031-3036.

[49] Gidding SS, Bookstein LC, Chomka EV. Usefulness of electron beam tomography in adolescents and young adults with heterozygous familial hypercholesterolemia. *Circulation*. 1998;98:2580-2583.

[50] Cuchel M, Bruckert E, Ginsberg HN, Raal FJ, Santos RD, Hegele RA, Kuivenhoven JA, Nordestgaard BG, Descamps OS, Steinhagen-Thiessen E, Tybjærg-Hansen A, Watts GF, Averna M, Boileau C, Boren J, Catapano AL, Defesche JC, Hovingh GK, Humphries SE, Kovanen PT, Masana L, Pajukanta P, Parhofer KG, Ray KK, Stalenhoef AF, Stroes E, Taskinen MR, Wiegman A, Wiklund O, Chapman MJ; European Atherosclerosis Society Consensus Panel on Familial Hypercholesterolaemia. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management: a position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. *Eur Heart J*. 2014;35:2146-2157. doi: 10.1093/eurheartj/ehu274.

[51] Haitas B, Baker SG, Meyer TE, Joffe BI, Seftel HC. Natural history and cardiac manifestations of homozygous familial hypercholesterolaemia. *Q J Med*. 1990;76:731-740.

[52] Raal FJ, Santos RD. Homozygous familial hypercholesterolemia: current perspectives on diagnosis and treatment. *Atherosclerosis*.

2012;223:262-268. doi: 10.1016/j.atherosclerosis.2012.02.019.

[53] Kawaguchi A, Yutani C, Yamamoto A. Hypercholesterolemic valvulopathy: an aspect of malignant atherosclerosis. *Ther Apher Dial*. 2003;7:439-443.

[54] Rader DJ, Cohen J, Hobbs HH. Monogenic hypercholesterolemia: new insights in pathogenesis and treatment. *J Clin Invest*. 2003;111:1795-1803. doi: 10.1172/JCI18925.

[55] Naoumova RP, Thompson GR, Soutar AK. Current management of severe homozygous hypercholesterolaemias. *Curr Opin Lipidol*. 2004;15:413-422.

[56] Watts GF, Gidding S, Wierzbicki AS, et al. Integrated guidance on the care of familial hypercholesterolaemia from the International FH Foundation. *Int J Cardiol* 2014;171:309-315.

[57] Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglu L, Wiklund O; ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41(1):111-188. doi: 10.1093/eurheartj/ehz455.

[58] Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC Jr, Sperling L, Virani SS, Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/

ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;73(24):3168-3209. doi: 10.1016/j.jacc.2018.11.002.

[59] Lui, D. T., Lee, A. C., & Tan, K. C. (2021). Management of Familial Hypercholesterolemia: Current Status and Future Perspectives. *Journal of the Endocrine Society*, 5(1), bvaa122.

[60] Goldberg AC, Hopkins PN, Toth PP, Ballantyne CM, Rader DJ, Robinson JG, Daniels SR, Gidding SS, de Ferranti SD, Ito MK, McGowan MP, Moriarty PM, Cromwell WC, Ross JL, Ziajka PE; National Lipid Association Expert Panel on Familial Hypercholesterolemia. Familial hypercholesterolemia: screening, diagnosis, and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol*. 2011;5(3 Suppl):S1-S8. doi: 10.1016/j.jacl.2011.04.003.

[61] Wiegman A, Gidding SS, Watts GF, Chapman MJ, Ginsberg HN, Cuchel M, Ose L, Averna M, Boileau C, Borén J, Bruckert E, Catapano AL, Defesche JC, Descamps OS, Hegele RA, Hovingh GK, Humphries SE, Kovanen PT, Kuivenhoven JA, Masana L, Nordestgaard BG, Pajukanta P, Parhofer KG, Raal FJ, Ray KK, Santos RD, Stalenhoef AF, Steinhagen-Thiessen E, Stroes ES, Taskinen MR, Tybjærg-Hansen A, Wiklund O; European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. *Eur Heart J*. 2015;36(36):2425-37. doi: 10.1093/eurheartj/ehv157.

[62] Santos RD. Screening and management of familial

hypercholesterolemia. *Curr Opin Cardiol*. 2019;34(5):526-530. doi: 10.1097/HCO.0000000000000660.

[63] Luirink IK, Wiegman A, Kusters DM, Hof MH, Groothoff JW, de Groot E, Kastelein JJP, Hutten BA. 20-Year Follow-up of Statins in Children with Familial Hypercholesterolemia. *N Engl J Med*. 2019;381(16):1547-1556. doi: 10.1056/NEJMoa1816454.

[64] Braamskamp MJ, Kusters DM, Avis HJ, Smets EM, Wijburg FA, Kastelein JJ, Wiegman A, Hutten BA. Long-term statin treatment in children with familial hypercholesterolemia: more insight into tolerability and adherence. *Paediatr Drugs*. 2015;17(2):159-166. doi: 10.1007/s40272-014-0116-y.

[65] Pang J, Chan DC, Watts GF. The Knowns and Unknowns of Contemporary Statin Therapy for Familial Hypercholesterolemia. *Curr Atheroscler Rep*. 2020;22(11):64. doi: 10.1007/s11883-020-00884-2.

[66] Raal FJ, Honarpour N, Blom DJ, Hovingh GK, Xu F, Scott R, Wasserman SM, Stein EA; TESLA Investigators. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2015;385(9965):341-350. doi: 10.1016/S0140-6736(14)61374-X.

[67] Sturm AC, Knowles JW, Gidding SS, Ahmad ZS, Ahmed CD, Ballantyne CM, Baum SJ, Bourbon M, Carrié A, Cuchel M, de Ferranti SD, Defesche JC, Freiburger T, Hershberger RE, Hovingh GK, Karayan L, Kastelein JJP, Kindt I, Lane SR, Leigh SE, Linton MF, Mata P, Neal WA, Nordestgaard BG, Santos RD, Harada-Shiba M, Sijbrands EJ, Stitzel NO, Yamashita S, Wilemon KA, Ledbetter DH, Rader DJ; Convened by the Familial Hypercholesterolemia Foundation.

Clinical Genetic Testing for Familial Hypercholesterolemia: JACC Scientific Expert Panel. *J Am Coll Cardiol*. 2018;72(6):662-680. doi: 10.1016/j.jacc.2018.05.044. PMID: 30071997.

[68] Hopkins PN, Defesche J, Fouchier SW, Bruckert E, Luc G, Cariou B, Sjouke B, Leren TP, Harada-Shiba M, Mabuchi H, Rabès JP, Carrié A, van Heyningen C, Carreau V, Farnier M, Teoh YP, Bourbon M, Kawashiri MA, Nohara A, Soran H, Marais AD, Tada H, Abifadel M, Boileau C, Chanu B, Katsuda S, Kishimoto I, Lambert G, Makino H, Miyamoto Y, Pichelin M, Yagi K, Yamagishi M, Zair Y, Mellis S, Yancopoulos GD, Stahl N, Mendoza J, Du Y, Hamon S, Krempf M, Swergold GD. Characterization of Autosomal Dominant Hypercholesterolemia Caused by PCSK9 Gain of Function Mutations and Its Specific Treatment With Alirocumab, a PCSK9 Monoclonal Antibody. *Circ Cardiovasc Genet*. 2015;8(6):823-831. doi: 10.1161/CIRCGENETICS.115.001129.

[69] Raal FJ, Hovingh GK, Blom D, Santos RD, Harada-Shiba M, Bruckert E, Couture P, Soran H, Watts GF, Kurtz C, Honarpour N, Tang L, Kasichayanula S, Wasserman SM, Stein EA. Long-term treatment with evolocumab added to conventional drug therapy, with or without apheresis, in patients with homozygous familial hypercholesterolaemia: an interim subset analysis of the open-label TAUSSIG study. *Lancet Diabetes Endocrinol*. 2017;5(4):280-290. doi: 10.1016/S2213-8587(17)30044-X.

[70] Hollman G, Gullberg M, Ek AC, Eriksson M, Olsson AG. Quality of life in patients with familial hypercholesterolaemia. *J Intern Med* 2002; 251: 331-337.

[71] Marteau T, Senior V, Humphries SE et al.; Genetic Risk Assessment for

FH Trial Study Group. Psychological impact of genetic testing for familial hypercholesterolemia within a previously aware population: a randomized controlled trial. *Am J Med Genet A* 2004; 128A: 285-293.

[72] Pappolla MA, Ros E, Sambamurti K, et al. O1-01-08: Cognitive impairment in heterozygous familial hypercholesterolemia Alzheimer's & Dementia. *J Alzheimer's Assoc* 2008, 4: T108.

[73] Zambón D, Quintana M, Mata P, Alonso R, Benavent J, Cruz-Sánchez F, Gich J, Pocoví M, Civeira F, Capurro S, Bachman D, Sambamurti K, Nicholas J, Pappolla MA. Higher incidence of mild cognitive impairment in familial hypercholesterolemia. *Am J Med*. 2010;123(3):267-274. doi: 10.1016/j.amjmed.2009.08.015.

[74] Ariza M, Cuenca N, Mauri M, Jurado MA, Garolera M. Neuropsychological performance of young familial hypercholesterolemia patients. *Eur J Intern Med*. 2016;34:e29-e31. doi: 10.1016/j.ejim.2016.05.009.

[75] Hyttinen L, TuulioHenriksson A, Vuorio AF, Kuosmanen N, Härkänen T, Koskinen S, Strandberg TE. Long-term statin therapy is associated with better episodic memory in aged familial hypercholesterolemia patients in comparison with population controls. *J Alzheimers Dis*. 2010;21(2):611-617. doi: 10.3233/JAD-2010-091381.

[76] Mauri M, Cuenca N, Borrallo RM, et al. Episodic memory performance in young adults with familial hypercholesterolemia. *Atherosclerosis* 2016, 252: e32.

[77] Claassen L, Henneman L, Kindt I, Marteau TM, Timmermans DR. Perceived risk and representations of cardiovascular disease and preventive behaviour in people diagnosed with familial hypercholesterolemia: a

cross-sectional questionnaire study. *J Health Psychol.* 2010;15(1):33-43. doi: 10.1177/1359105309345170.

[78] Frich JC, Ose L, Malterud K, Fugelli P. Perceived vulnerability to heart disease in patients with familial hypercholesterolemia: a qualitative interview study. *Ann Fam Med.* 2006;4:198-204. doi: 10.1370/afm.529.

[79] Claassen L, Henneman L, van der Weijden T, Marteau TM, Timmermans DR. Being at risk for cardiovascular disease: perceptions and preventive behavior in people with and without a known genetic predisposition. *Psychol Health Med.* 2012;17:511-521. doi: 10.1080/13548506.2011.644246.

[80] Senior V, Marteau TM, Weinman J; Genetic Risk Assessment for FH Trial (GRAFT) Study Group. Self-reported adherence to cholesterol-lowering medication in patients with familial hypercholesterolaemia: the role of illness perceptions. *Cardiovasc Drugs Ther* 2004; 18: 475-481.

[81] Hagger MS, Hardcastle SJ, Hingley C, Strickland E, Pang J, Watts GF. Predicting Self-Management Behaviors in Familial Hypercholesterolemia Using an Integrated Theoretical Model: the Impact of Beliefs About Illnesses and Beliefs About Behaviors. *Int J Behav Med.* 2016;23(3):282-294. doi: 10.1007/s12529-015-9531-x.

[82] Umans-Eckenhausen MA, Defesche JC, van Dam MJ, Kastelein JJ. Long-term compliance with lipid-lowering medication after genetic screening for familial hypercholesterolemia. *Arch Intern Med.* 2003;163:65-68. doi:10.1001/archinte.163.1.65

[83] Leren TP, Manshaus T, Skovholt U, Skodje T, Nossen IE, Teie C, Sørensen S, Bakken KS. Application of molecular genetics for diagnosing familial

hypercholesterolemia in Norway: results from a family-based screening program. *Semin Vasc Med.* 2004;4(1):75-85. doi: 10.1055/s-2004-822989.

[84] Leren TP. Cascade genetic screening for familial hypercholesterolemia. *Clin Genet.* 2004; 66:483-487. doi:10.1111/j.1399-0004.2004.00320.x

[85] Umans-Eckenhausen MA, Defesche JC, Sijbrands EJ, Scheerder RL, Kastelein JJ. Review of first 5 years of screening for familial hypercholesterolaemia in the Netherlands. *Lancet* 2001; 357:165-168. doi:10.1016/S0140-6736(00)03587-X