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Executive Summary

Familial Hypercholesterolemia: Screening, diagnosis and management of pediatric and adult patients

Clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia

Anne C. Goldberg, MD, FNLA, Chair*, Paul N. Hopkins, MD, MSPH, Peter P. Toth, MD, PhD, FNLA, Christie M. Ballantyne, MD, FNLA, Daniel J. Rader, MD, FNLA, Jennifer G. Robinson, MD, MPH, FNLA, Stephen R. Daniels, MD, PhD, Samuel S. Gidding, MD, Sarah D. de Ferranti, MD, MPH, Matthew K. Ito, PharmD, FNLA, Mary P. McGowan, MD, FNLA, Patrick M. Moriarty, MD, William C. Cromwell, MD, FNLA, Joyce L. Ross, MSN, CRNP, FNLA, Paul E. Ziajka, MD, PhD, FNLA

Washington University Medical School, St. Louis, MO, USA (Dr. Goldberg); Cardiovascular Disease Risk Reduction Clinic, University of Utah School of Medicine, Salt Lake City, UT, USA (Dr. Hopkins); Sterling Rock Falls Clinic, Ltd., CGH Medical Center, University of Illinois School of Medicine, Sterling, IL, USA (Dr. Toth); Section of Atherosclerosis and Vascular Medicine, Center for Cardiovascular Disease Prevention, Baylor College of Medicine, Houston, TX, USA (Dr. Ballantyne); University of Pennsylvania, Philadelphia, PA, USA (Dr. Rader); University of Iowa, Lipid Research Clinic, Prevention Intervention Center, University of Iowa, Iowa City, IA, USA (Dr. Robinson); Department of Pediatrics, University of Colorado School of Medicine, The Children's Hospital, Aurora, CO, USA (Dr. Daniels); Nemours Cardiac Center, A.I. DuPont Hospital for Children, Wilmington, DE, USA (Dr. Gidding); Preventive Cardiology, Children's Hospital Boston, Harvard Medical School, Boston, MA, USA (Dr. de Ferranti); Oregon State University/Oregon Health & Science University, Portland, OR, USA (Dr. Ito); Cholesterol Treatment Center, Concord Hospital, Concord, NH, USA (Dr. McGowan); University of Kansas Medical Center, Kansas City, KS, USA (Dr. Moriarty); Lipoprotein and Metabolic Disorders Institute, Wake Forest University School of Medicine, Raleigh, NC, USA (Dr. Cromwell); University of Pennsylvania Health System, Philadelphia, PA, USA (Dr. Ross); and Florida Lipid Institute, Winter Park, FL, USA (Dr. Ziajka)

* Corresponding author.
E-mail address: agoldber@dom.wustl.edu
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Abstract: The familial hypercholesterolemias (FH) are a group of genetic defects resulting in severe elevations of blood cholesterol levels and increased risk of premature coronary heart disease. FH is among the most commonly occurring congenital metabolic disorders. FH is a treatable disease. Aggressive lipid lowering is necessary to achieve the target LDL cholesterol reduction of at least 50% or more. Even greater target LDL cholesterol reductions may be necessary for FH patients who have other CHD risk factors. Despite the prevalence of this disease and the availability of effective treatment options, FH is both underdiagnosed and undertreated, particularly among children. Deficiencies in the diagnosis and treatment of FH indicate the need for greatly increased awareness and understanding of this disease, both on the part of the public and of healthcare practitioners. This document provides recommendations for the screening, diagnosis and treatment of FH in pediatric and adult patients developed by the National Lipid Association Expert Panel on Familial Hypercholesterolemia. This report goes beyond previously published guidelines by providing specific clinical guidance for the primary care clinician and lipid specialist with the goal of improving care of patients with FH and reducing their elevated risk for CHD.

Background and rationale

The familial hypercholesterolemias (FH) are a group of genetic defects resulting in severe elevations of blood cholesterol levels. Although the term FH has, in the past, been used to refer specifically to LDL receptor (LDLR) defects, this document will use a broader definition to reflect discoveries of defects in the genes for apolipoprotein (Apo) B, proprotein convertase subtilisin/kexin type 9 (PCSK9), and possibly others yet to be described, which produce severe hypercholesterolemia and increased risk of premature coronary heart disease (CHD). Total cholesterol concentrations in heterozygous FH patients (genetic defect inherited from one parent) are typically in the range of 350 to 550 mg/dL and in homozygotes (genetic defects inherited from both parents) range from 650 to 1000 mg/dL. FH is among the most commonly occurring congenital metabolic disorders. The heterozygous form occurs in approximately 1 in 300 to 500 people in many populations, although this ratio is much higher in certain populations in the U.S. The homozygous form is quite rare, occurring in approximately 1 out of every 1,000,000 individuals. Because FH is due to a genetic defect or defects, hypercholesterolemia is present from childhood, leading to early development of CHD. Of particular concern are FH homozygotes, in whom the severity of hypercholesterolemia usually results in severe atherosclerosis and even cardiovascular disease during childhood and adolescence.

FH is a treatable disease. Aggressive lipid lowering is necessary to achieve the target LDL cholesterol reduction of at least 50% or more. Even greater target LDL cholesterol reductions may be necessary for FH patients who have other CHD risk factors. In addition to diet and lifestyle modifications, safe and effective medical therapies are available, including statins and other lipid-lowering drugs, and LDL apheresis, (a method of removing LDL and other Apo B particles from the blood). Despite the prevalence of this disease and the availability of effective treatment options, FH is both underdiagnosed and undertreated, particularly among children. Some estimates suggest that approximately 20% of patients are diagnosed and, of those, only a small minority receive appropriate treatment.

Deficiencies in the diagnosis and treatment of FH indicate the need for greatly increased awareness and understanding of this disease, both on the part of the public and of healthcare practitioners. Central to that education is comprehension of the importance of universal screening during childhood and cascade lipid screening of family members of known FH patients. This document provides recommendations for the screening, diagnosis and treatment of FH in pediatric and adult patients (including women of childbearing potential and during pregnancy) developed by the National Lipid Association Expert Panel on Familial Hypercholesterolemia. This report goes beyond previously published guidelines by providing specific clinical guidance for the primary care clinician and lipid specialist with the goal of improving care of patients with FH and reducing their elevated risk for CHD. The rationale and supporting evidence for these recommendations are published separately in a supplement,[1–5] but are not intended to be a comprehensive examination of the published literature.

1. Definition, prevalence, genetics, diagnosis and screening

1.1 Definition of familial hypercholesterolemias

1.1.1 The FH are a group of inherited genetic defects resulting in severely elevated serum cholesterol concentrations.

1.1.2 For purposes of this document, FH will refer to the autosomal dominant forms of severe hypercholesterolemia unless otherwise specified. However, causes of inherited high cholesterol are not restricted to autosomal dominant FH.

1.2 Prevalence of FH and associated risk

1.2.1 The prevalence of FH is 1 in 300 to 500 in many populations, making FH among the most common of serious genetic disorders.

1.2.2 There are approximately 620,000 FH patients currently living in the United States.
1.2.3 The risk of premature coronary heart disease (CHD) is elevated about 20-fold in untreated FH patients.
1.2.4 Approximately 1 in one million persons is homozygous (or compound heterozygous) for *LDLR* mutations and has extreme hypercholesterolemia with rapidly accelerated atherosclerosis when left untreated.
1.2.5 In a few populations (such as French Canadians and Dutch Afrikaners), the prevalence of FH may be as high as 1 in 100.

1.3 Genetics of FH

1.3.1 Currently, known causes of FH include mutations in the LDL receptor (*LDLR*), Apo B (*APOB*), or proprotein convertase subtilisin/kexin type 9 (*PCSK9*) genes.
1.3.2 There are over 1600 known mutations of the *LDLR* gene documented to cause FH at the time of this writing, accounting for about 85 to 90% of FH cases.
1.3.3 The Arg3500Gln mutation in *APOB* is the most common cause of hypercholesterolemia due to an *APOB* mutation, accounting for 5 to 10% of FH cases in Northern European populations (rare in other populations).
1.3.4 Gain-of-function mutations in *PCSK9* cause fewer than 5% of cases in most studies.

1.4 Screening for FH

1.4.1 Universal screening for elevated serum cholesterol is recommended. FH should be suspected when untreated fasting LDL cholesterol or non-HDL cholesterol levels are at or above the following:
- Adults (≥20 years): LDL cholesterol ≥190 mg/dL or non-HDL cholesterol ≥220 mg/dL;
- Children, adolescents and young adults (<20 years): LDL cholesterol ≥160 mg/dL or non-HDL cholesterol ≥190 mg/dL.

1.4.2 For all individuals with these levels, a family history of high cholesterol and heart disease in first-degree relatives should be collected. The likelihood of FH is higher in individuals with a positive family history of hypercholesterolemia or of premature CHD (onset in men before age 55 years and women before age 65 years).
1.4.3 Cholesterol screening should be considered beginning at age 2 for children with a family history of premature cardiovascular disease or elevated cholesterol. All individuals should be screened by age 20.
1.4.4 Although not present in many individuals with FH, the following physical findings should prompt the clinician to strongly suspect FH and obtain necessary lipid measurements if not already available:
- Tendon xanthomas at any age (most common in Achilles tendon and finger extensor tendons, but can also occur in patellar and triceps tendons).
- Arcus corneae in a patient under age 45.
- Tuberous xanthomas or xanthelasma in a patient under age 20 to 25.

1.4.5 At the LDL cholesterol levels listed below the probability of FH is approximately 80% in the setting of general population screening. These LDL cholesterol levels should prompt the clinician to *strongly* consider a diagnosis of FH and obtain further family information:
- LDL cholesterol ≥250 mg/dL in a patient aged 30 or more;
- LDL cholesterol ≥220 mg/dL for patients aged 20 to 29;
- LDL cholesterol ≥190 mg/dL in patients under age 20.

1.5 Diagnosis

1.5.1 Age at onset of CHD, even if approximate, is particularly important to note in the family history.
1.5.2 Physical signs of FH are insensitive but can be quite specific. The presence of tendon xanthomas should be sought for by careful palpation (not just visual inspection) of the Achilles tendon and finger extensor tendons. Corneal arcus (partial or complete) is only indicative of FH if present under age 45. Neither xanthelasma nor tuberous xanthomas are specific for FH but, if they are encountered in a younger patient, FH should be considered. Importantly, the absence of any of these physical findings does not rule out FH.
1.5.3 Formal clinical diagnosis of FH can be made by applying any one of several validated sets of criteria [U.S. Make Early Diagnosis Prevent Early Death (MEDPED), Dutch Lipid Clinic Network, Simon-Broome Registry]. It should be noted that LDL cholesterol cut points usually vary with age.
1.5.4 The clinical diagnosis of FH is most likely when two or more first-degree relatives are found to have elevated LDL cholesterol in the range noted above, when pediatric cases are identified in the family, or when the patient or a close relative has tendon xanthomas.
1.5.5 Once a family is diagnosed with FH, somewhat lower LDL cholesterol cut points can be applied to identify additional affected family members.
1.5.6 Patients with FH occasionally have elevated triglycerides, and high triglycerides should not exclude the diagnosis of FH.

1.6 Genetic screening

1.6.1 Genetic screening for FH is generally not needed for diagnosis or clinical management but may be useful when the diagnosis is uncertain.

1.6.2 Identification of a causal mutation may provide additional motivation for some patients to implement appropriate treatment.

1.6.3 Importantly, a negative genetic test does not exclude FH, since approximately 20% of clinically definite FH patients will not be found to have a mutation despite an exhaustive search using current methods.

1.7 Cascade screening

1.7.1 Cascade screening involves testing lipid levels in all first-degree relatives of diagnosed FH patients.

1.7.2 As cascade screening proceeds, newly identified FH cases provide additional relatives who should be considered for screening.

1.7.3 Cascade screening is the most cost-effective means of finding previously undiagnosed FH patients and is also cost-effective in terms of cost per year of life saved. General population screening of a young population (before age 16) is similarly cost-effective in terms of cost per year of life saved, given that effective cholesterol-lowering treatment is begun in all those identified.

2. Adult treatment recommendations and evidence for treatment

2.1 Rationale for treatment

2.1.1 Individuals with FH have a very high lifetime risk of CHD and are at very high risk of premature onset CHD.

2.1.2 Early treatment is highly beneficial. Long-term drug therapy of patients with FH can substantially reduce or remove the excess lifetime risk of CHD due to the genetic disorder and can lower CHD event rates in FH patients to levels similar to those of the general population.

2.1.3 FH requires lifelong treatment and regular follow-up.

2.2 Treatment

2.2.1 Both children and adults with LDL cholesterol $\geq$190 mg/dL [or non-high-density lipoprotein (HDL) cholesterol $\geq$220 mg/dL] after lifestyle changes will require drug therapy.

2.2.2 For adult FH patients ($\geq$20 years of age), drug treatment to achieve an LDL cholesterol reduction $\geq$50% should be initiated.

2.2.3 Statins should be the initial treatment for all adults with FH.

2.3 Intensified drug treatment

2.3.1 Higher risk patients may need intensification of drug treatment to achieve more aggressive treatment goals (LDL cholesterol $<$100 mg/dL and non-HDL cholesterol $<$130 mg/dL).

2.3.2 Any of the following places FH patients at higher CHD risk: clinically evident CHD or other atherosclerotic cardiovascular disease, diabetes, a family history of very early CHD (in men $<$45 years of age and women $<$55 years of age), current smoking, two or more CHD risk factors, or high lipoprotein (a) $\geq$50 mg/dL using an isoform insensitive assay.

2.3.3 In FH patients without any of the characteristics listed above, intensification of drug therapy may be considered if LDL cholesterol remains $\geq$160 mg/dL (or non-HDL cholesterol $\geq$190 mg/dL), or if an initial 50% reduction in LDL cholesterol is not achieved.

2.3.4 Ezetimibe, niacin, and bile acid sequestrants are reasonable treatment options for intensification of therapy, or for those intolerant of statins.

2.3.5 The potential benefit of multidrug regimens for an individual patient should be weighed against the increased cost and potential for adverse effects and decreased adherence.

2.4 Risk factors should be aggressively treated

2.4.1 Risk factors are the same in FH as in the general population and require aggressive management to reduce CHD risk, with special attention to smoking cessation.

2.4.2 Regular physical activity, a healthy diet and weight control should be emphasized.

2.4.3 Blood pressure should be treated to $<$140/90 mm Hg (or $<$130/80 mm Hg in those with diabetes). Low dose aspirin (75-81 mg per day) should be considered in those at high CHD or stroke risk.

2.5 Risk stratification algorithms should not be used

2.5.1 Individuals with FH are at high CHD risk. The 10-year CHD risk in the FH patient is not adequately predicted by any conventional risk assessment tools. Therefore, assessment of 10-year risk is not recommended.

2.5.2 All FH patients require lifestyle management, and very few will not require lipid-lowering drug therapy.

2.6 Consider referral to a lipid specialist

2.6.1 Consider referral to a lipid specialist with expertise in FH if LDL cholesterol concentrations are not reduced by $\geq$50% or if patients are at high risk.

2.6.2 Cascade testing of first-degree relatives should be offered to all individuals with FH.

3. Management issues in pediatrics

3.1 Screening

3.1.1 Universal screening at age 9 to 11 years with a fasting lipid profile or nonfasting non-HDL cholesterol measurement is recommended to identify all children with FH. This age identifies individuals at the potential onset of advanced atherosclerosis, and provides the best discrimination between those with and without inherited dyslipidemias by avoiding confounding due to changes in lipid levels associated with puberty.

3.1.2 If a nonfasting non-HDL cholesterol concentration of ≥145 mg/dL is detected, then a fasting lipid profile should be performed.

3.1.3 Screening should occur earlier (≥2 years of age) in the presence of a positive family history for hypercholesterolemia or premature CHD or the presence of other major CHD risk factors.

3.1.4 Identifying FH in someone with other major CHD risk factors is critical for risk stratification.

3.1.5 Evaluation (history, physical examination, selected laboratory tests) of possible secondary causes of dyslipidemia should be performed. Secondary causes include hypothyroidism, nephrotic syndrome, and liver disease.

3.2 Diagnosis

3.2.1 Untreated fasting lipid levels at which FH may be suspected in children, adolescents and young adults (<20 years) are LDL cholesterol concentration ≥160 mg/dL or non-HDL cholesterol ≥190 mg/dL. These levels are supported by family studies of affected individuals.

3.2.2 A second lipid profile should be performed to assess response to diet management, to account for regression to the mean, and to accurately classify those with levels close to classification thresholds.

3.3 Lipid specialists

3.3.1 Primary care clinicians should be responsible for screening and diagnosis.

3.3.2 For treatment of children with FH, either consultation with or referral to a lipid specialist is recommended. Pediatric lipid specialists include pediatric cardiologists, endocrinologists, or other health care providers with specialized lipidology training. Use of lipid lowering medications is currently not typically part of pediatric training.

3.3.3 Homozygous FH should always be managed by a lipid specialist.

3.4 Cardiovascular risk assessment

3.4.1 Comprehensive CHD risk assessment [including measurement of lipoprotein (a) levels] and management is critical. The presence of multiple CHD risk factors is associated with dramatic acceleration of atherosclerosis development.

3.4.2 Primordial prevention, which includes counseling for the prevention of risk development (not smoking, low saturated fat diet, appropriate caloric intake and regular physical activity supporting the avoidance of diabetes), is an important component of treatment of patients with FH.

3.5 Treatment in children

3.5.1 Statins are preferred for initial pharmacologic treatment in children after initiation of diet and physical activity management.

3.5.2 Consideration should be given to starting treatment at the age of 8 years or older. In special cases, such as those with homozygous FH, treatment might need to be initiated at earlier ages.

3.5.3 Clinical trials with medium term follow up suggest safety and efficacy of statins in children.

3.5.4 The treatment goal of lipid lowering therapy in pediatric FH patients is a ≥50% reduction in LDL cholesterol or LDL cholesterol <130 mg/dL. There is a need in treatment of pediatric FH for balance between increased dosing and the potential for side effects vs. achieving goals. More aggressive LDL cholesterol targets should be considered for those with additional CHD risk factors.

3.6 Homozygous FH

3.6.1 Initiation of therapy early in life and ongoing monitoring of homozygous FH is vital.

3.6.2 High dose statins may be effective in some homozygous FH patients, but the majority will require LDL apheresis. Liver transplantation is also being used in some centers.

3.6.3 Gene therapy is a potential new treatment in development and may be particularly beneficial for homozygous FH patients.

4. Management issues in adults

4.1 Lifestyle modifications

4.1.1 Patients with FH should be counseled regarding the following lifestyle modifications:

- Therapeutic Lifestyle Changes and dietary adjuncts.
  - Reduced intakes of saturated fats and cholesterol: total fat 25–35% of energy intake, saturated fatty acids <7% of energy intake, dietary cholesterol <200 mg/d.
  - Use of plant stanol or sterol esters 2 g/d.
  - Use of soluble fiber 10-20 g/d.
- Physical activity and caloric intake to achieve and maintain a healthy body weight.
- Limitation of alcohol consumption.
- Emphatic recommendation to avoid use of any tobacco products.

4.1.2 Clinicians are encouraged to refer patients to registered dietitians or other qualified nutritionists for medical nutrition therapy.

4.2 Drug treatment of FH

4.2.1 For adult FH patients, initial treatment is the use of moderate to high doses of high-potency statins titrated to achieve an LDL cholesterol reduction ≥50% from baseline. Low potency statins are generally inadequate for FH patients.

4.2.2 If the initial statin is not tolerated, consider changing to an alternative statin, or every-other-day statin therapy.

4.2.3 If initial statin therapy is contraindicated or poorly tolerated, ezetimibe, a bile acid sequestrant (colesevelam), or niacin may be considered.

4.2.4 For patients who cannot use a statin, most will require combination drug therapy.

4.3 Additional treatment considerations

4.3.1 If the patient is not at LDL cholesterol treatment goal with the maximum available and tolerable dose of statin, then combine with ezetimibe, niacin, or a bile acid sequestrant (colesevelam preferred).

4.3.2 Decisions regarding selection of additional drug combinations should be based on concomitant risk factors for myopathy, concomitant medications, and the presence of other disease conditions and lipid abnormalities.

4.4 Candidates for LDL apheresis

4.4.1 LDL apheresis is a U.S. Food and Drug Administration approved medical therapy for patients who are not at LDL cholesterol treatment goal or who have ongoing symptomatic disease.

4.4.2 In patients who, after six months, do not have an adequate response to maximum tolerated drug therapy, LDL apheresis is indicated according to these guidelines:

- Functional homozygous FH patients with LDL cholesterol ≥300 mg/dL (or non-HDL-C ≥330 mg/dL).
- Functional heterozygous FH patients with LDL cholesterol ≥300 mg/dL (or non-HDL-C ≥330 mg/dL) and 0-1 risk factors.
- Functional heterozygous FH patients with LDL cholesterol ≥200 mg/dL (or non-HDL-C ≥230 mg/dL) and high risk characteristics such as ≥2 risk factors or high lipoprotein (a) ≥50 mg/dL using an isoform insensitive assay.
- Functional heterozygotes with LDL cholesterol ≥160 mg/dL (or non-HDL-C ≥190 mg/dL) and very high-risk characteristics (established CHD, other cardiovascular disease, or diabetes).

4.5 LDL apheresis referrals

4.5.1 Healthcare practitioners should refer candidates for LDL apheresis to qualified sites. Self-referrals are also possible. A list of sites qualified to perform LDL apheresis is in development and will be posted on the National Lipid Association website (www.lipid.org).

4.6 Women of childbearing age

4.6.1 Women with FH should receive pre-pregnancy counseling and instructions to stop statins, ezetimibe, and niacin at least four weeks before discontinuing contraception and should not use these medications during pregnancy and lactation.

4.6.2 Consultation with her healthcare practitioner regarding continuation of any other lipid medications is recommended.

4.6.3 In case of unintended pregnancy, a woman with FH should discontinue statins, ezetimibe, and niacin immediately and should consult with her healthcare practitioner promptly.

4.7 Treatment options during pregnancy

4.7.1 Statins, ezetimibe, and niacin should not be used during pregnancy. Use of other lipid lowering medications (e.g., colesevelam) may be considered under the guidance of the healthcare practitioner.

4.7.2 Consider LDL apheresis during pregnancy if there is significant atherosclerotic disease or if the patient has homozygous FH.

4.8 Hard to manage patients

4.8.1 If other treatment options are inadequate or the FH patient cannot tolerate pharmacotherapy or LDL apheresis, other treatment options include ileal bypass and liver transplantation (both are used rarely), and, potentially, new drugs in development.

5. Future issues, public policy, and public awareness

5.1 Screening

5.1.1 It is the responsibility of all primary health care providers and relevant specialists to screen all children and adults for hypercholesterolemia, and to initiate therapy in patients with FH and severe hypercholesterolemia.

5.2 Lipid specialists

5.2.1 Patients with FH who do not respond adequately to, or are intolerant of, initial statin therapy should be referred to a lipid specialist.

5.2.2 For children with FH, either consultation with or referral to a lipid specialist is recommended.

5.2.3 Patients who are candidates for more intensive therapy, or who have family histories of very

premature CHD (in men <45 years of age and women <55 years of age), should also be referred to a lipid specialist.

5.3 Payers

5.3.1 Patients with FH are at high lifetime risk of atherosclerotic cardiovascular disease and appropriate therapy is required.

5.3.2 Payers should cover initial screening, initiation of therapy with appropriate medications, and monitoring of response to therapy.

5.3.3 Payers should cover appropriate drugs including high potency statins and combination lipid drug therapy. They should also cover other drugs and combinations for patients with statin tolerance problems.

5.3.4 LDL apheresis and genetic testing, when appropriate, should be covered by payers.

5.4 Public and provider awareness

5.4.1 To promote early diagnosis of FH and the prevention, and treatment of CHD, public awareness of FH needs to be increased by a variety of methods.

5.4.2 Health care provider awareness needs to be increased through education at all levels and in multiple specialties, through partnering with professional organizations and through local, national and international health agencies.

5.5 Responsibility for education

5.5.1 Health systems, hospitals, pharmacy benefits management organizations, and insurance companies should contribute to patient and provider education.

5.5.2 Governmental agencies and other policy makers at local, state, national and international levels should be engaged in efforts to screen and treat FH.

5.6 Research needs

5.6.1 Research is needed in the following areas related to FH:

- Agents to further lower LDL cholesterol;
- Ways to improve adherence to and persistence with therapy;
- Cost effective genetic screening;
- Behavioral management of patients with FH;
- Cost effectiveness analysis of various approaches to screening and treatment;
- Cost effectiveness analysis of the benefits of aggressive therapy;
- Long-term follow-up of patients with FH, including safety of long-term therapy with lipid lowering drugs;
- Differences in drug metabolism by gender, ethnicity, and age;
- Long-term cardiovascular benefits of combination therapies;
- Management of FH in pregnancy;
- Mechanism and management of statin intolerance;
- Safety and effectiveness of dietary supplements and dietary adjuncts for LDL cholesterol reduction;
- Methods to enhance healthcare provider adherence to guidelines.

5.7 Funding

5.7.1 Funding for FH education and research should come from multiple sources including government, professional associations, industry, and private donations.

Concluding statements

FH is a difficult to treat but manageable disease. Primary care clinicians should be aware of the key role they play in the early detection and treatment of FH, and of the availability of additional support and guidance from lipid specialists who have undergone intensive training in the management of lipid disorders. Key elements for control of FH include reducing the LDL cholesterol concentration, management of additional CHD risk factors, such as elevated blood pressure and smoking, and improving adherence to and persistence with lifestyle modifications and pharmacotherapy. Screening first-degree relatives of patients with FH, including siblings, parents and children, facilitates early detection and treatment. Long-term drug therapy of patients with FH significantly reduces or removes the excess lifetime risk of CHD, lowering the level of risk to that of the general population.

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