Familial hypercholesterolaemia in children and adolescents

a European Atherosclerosis Society consensus statement

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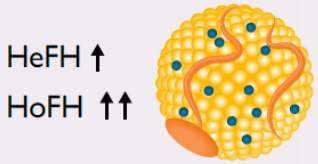
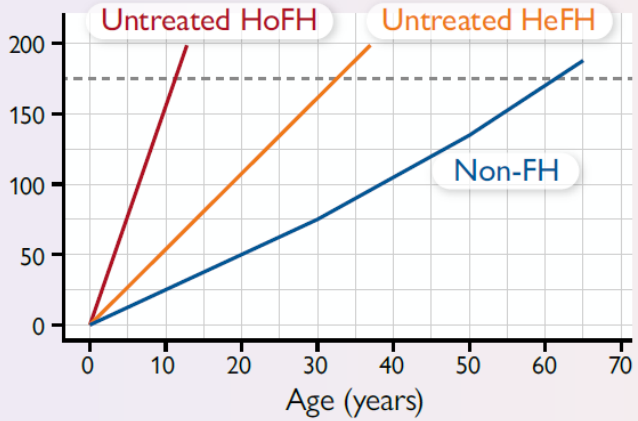
FH in children and adolescents

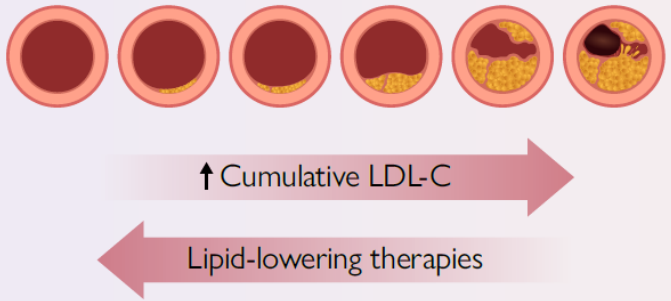
Characteristics of FH



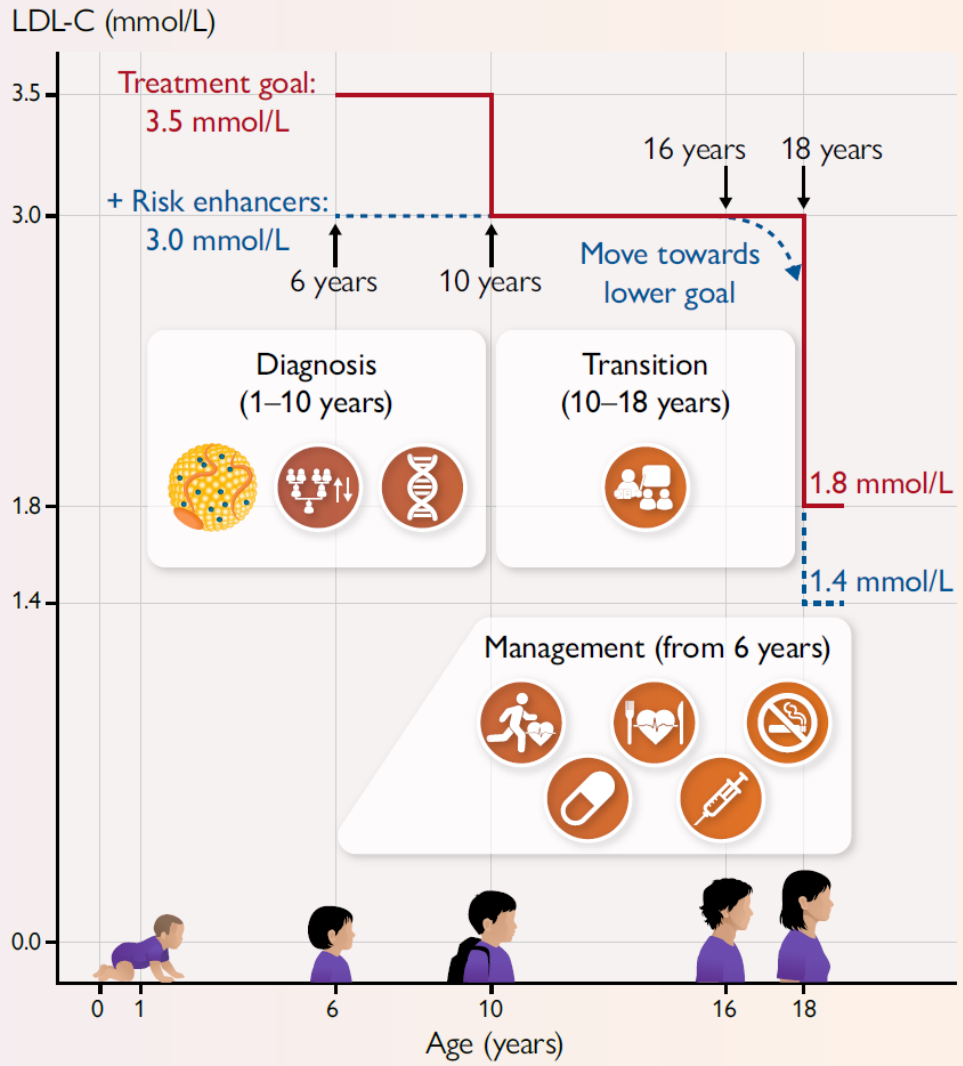
Cumulative LDL-C exposure (mmol/L × years)



Progression of atherosclerosis



Diagnosis and management of HeFH



FH, familial hypercholesterolaemia; **HeFH**, heterozygous familial hypercholesterolaemia; **HoFH**, homozygous familial hypercholesterolaemia; **LDL-C**, low-density lipoprotein cholesterol

Wiegman A, *et al. European Heart Journal.*

Understanding familial hypercholesterolaemia (FH)

1 in 300

Heterozygous FH (HeFH)
Common worldwide

1 in 250,000 – 1 in 360,000

Homozygous FH (HoFH)
Rare & severe

- Underdiagnosis remains a major issue
- Family cascade or universal screening programmes increase detection rate, but are not widely used
- Children should be diagnosed and appropriately treated in the first decade of life

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What is new in this EAS consensus statement on children with FH?

- Updated diagnostic criteria to improve diagnostic sensitivity
- Proposed lower age to start treatment
- Proposed lower LDL-C treatment goals, made possible by the availability of new LLTs
- Emphasis on the importance of reducing cumulative LDL-C exposure
- Updated treatment algorithms and the latest evidence supporting the use of novel LLTs
- Proposals to facilitate improved transition to adult care and implementation strategies

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Table 1 Comparison of the diagnostic criteria and LDL-C treatment goals proposed in the current consensus and in the 2015 EAS consensus statement for children with FH

2015	2026
Diagnostic criteria	Diagnostic criteria
Highly probable FH	**Clinical FH**
• LDL-C ≥5.0 mmol/L (190 mg/dL) measured twice after dietary intervention	• LDL-C >4.5 mmol/L (175 mg/dL)
• LDL-C ≥4.0 mmol/L (155 mg/dL) if family history of premature ASCVD and/or high baseline cholesterol in one parent	• LDL-C >3.5 mmol/L (135 mg/dL) if family history of premature ASCVD and/or high baseline cholesterol in one parent
• LDL-C ≥3.5 mmol/L (135 mg/dL) if one parent has a genetic diagnosis of FH	• LDL-C >3.0 mmol/L (115 mg/dL) if one parent has a genetic diagnosis of FH
Definite FH	**Definite FH**
• if a child has a genetic diagnosis of FH	• if a child has a genetic diagnosis of FH
LDL-C treatment goals	LDL-C treatment goals
Start pharmacological treatment at 8 years	Start pharmacological treatment ideally at 6 years
Reduce LDL-C concentration	**Reduce LDL-C concentration**
• by 50% from baseline at 8–10 years	• to ≤3.5 mmol/L (135 mg/dL) at 6–<10 years
• to 3.5 mmol/L (135 mg/dL) at >10–<18 years	• to ≤3.0 mmol/L (115 mg/dL) at 10–<18 years or with other major risk enhancers* at 6–<10 years

*Major risk enhancers: lipoprotein(a) ≥250 nmol/L (120 mg/dL) – a high concentration associated with a doubled risk of atherosclerotic cardiovascular disease (ASCVD) in the adult population; diabetes; hypertension; chronic inflammatory diseases; chronic kidney disease; Kawasaki disease; human immunodeficiency virus; cancer survivor.

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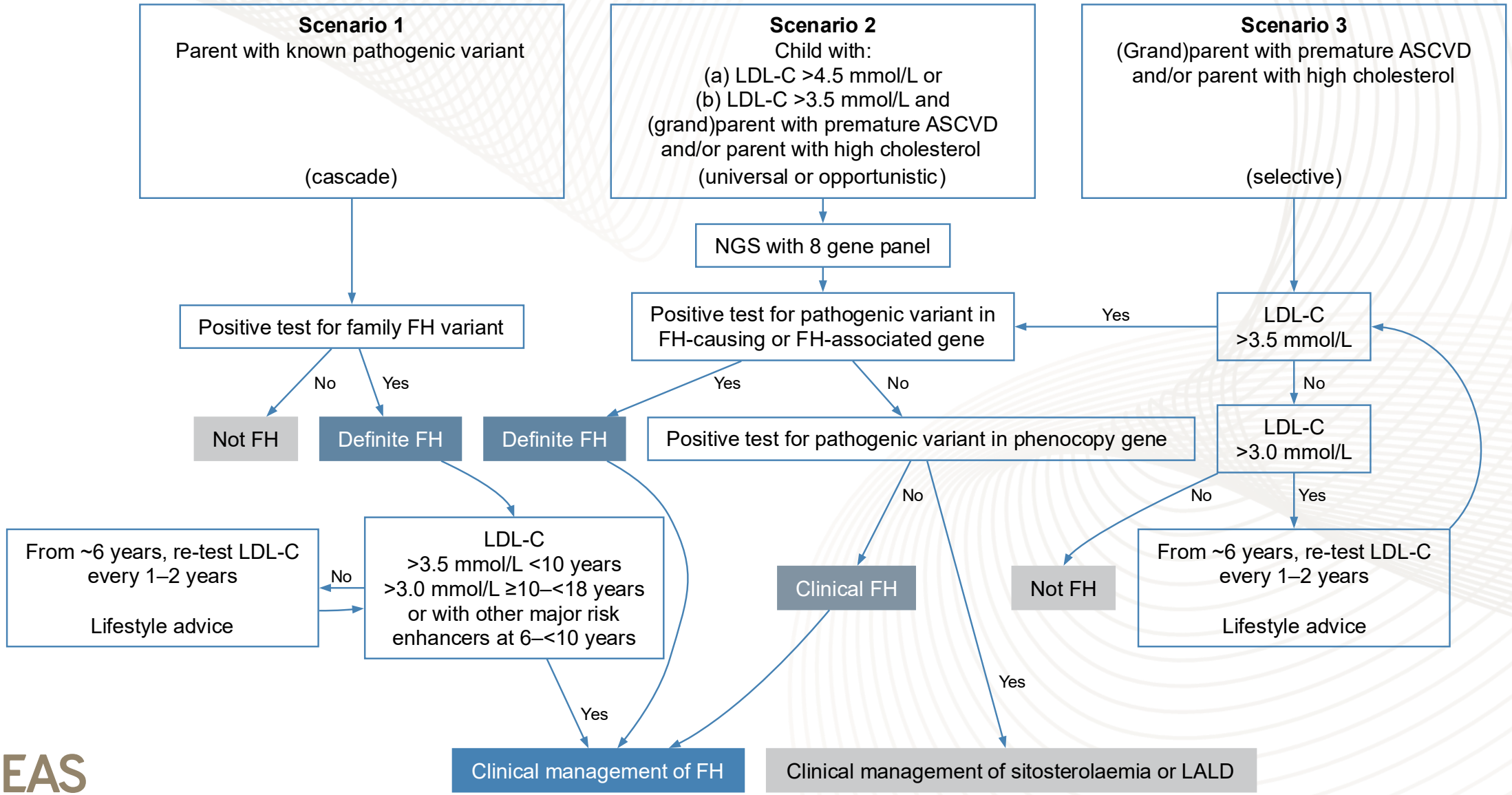
Entry points for diagnosis and clinical management of children suspected to have FH



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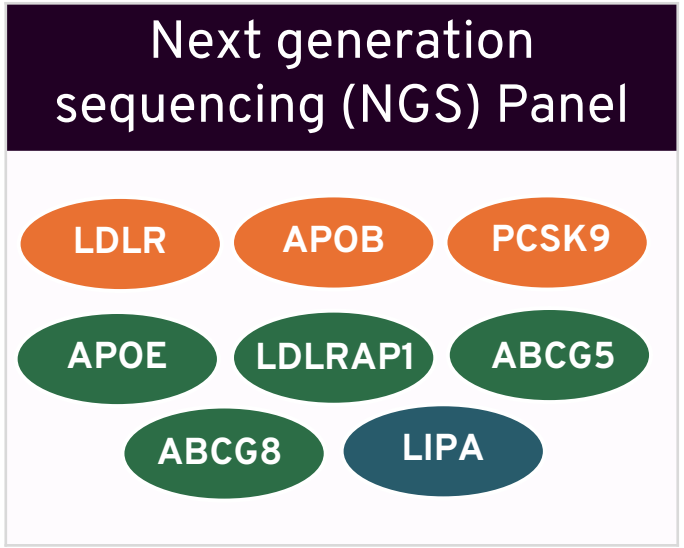
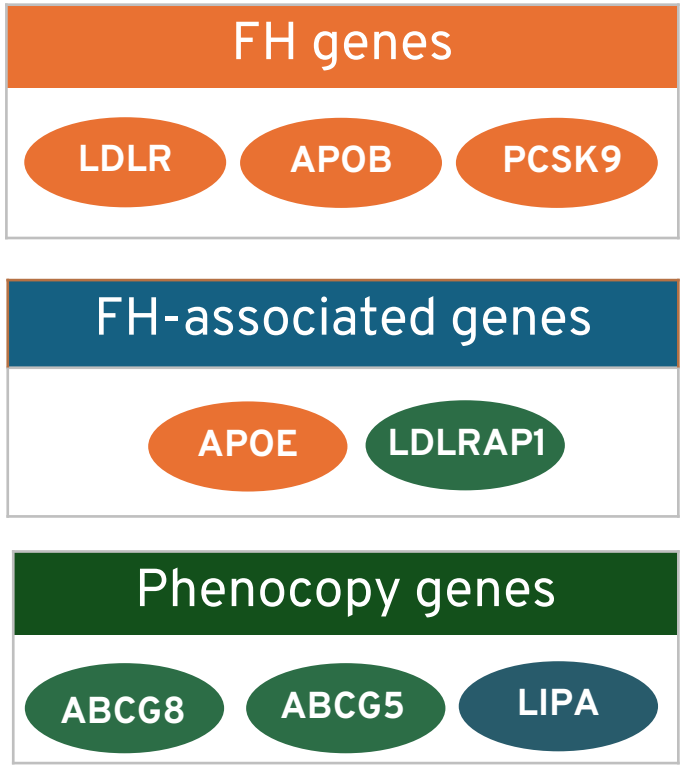
Genetic testing in children with suspected FH

NGS-based panel including FH genes and phenocopies





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Advantages and disadvantages of genetic testing for familial hypercholesterolaemia (FH)

Advantages of a confirmed genetic diagnosis of FH	Disadvantages
• Confirms definitive FH and establishes the FH diagnosis unequivocally	• Potential confusion of diagnosis if a variant of uncertain significance is found
• Supports the clinician when deciding which LLT to use	• Life and health insurance issues in some countries
• Helps the parents decide whether and when their child should start LLT	• Potential stigmatization
• Enables access to special therapies	• Psychological distress for individuals and their family
• Prompts testing of parents and siblings who are at 50% risk of carrying the FH-causing variant	
• Encourages cascade testing in the extended family	
• Creates awareness that FH is passed on to the next generation	
• Encourages adherence to LLT	
• Encourages adherence to a healthy lifestyle and not smoking/vaping	
• Creates awareness that atherosclerosis starts at birth	

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Genetic counselling as the foundation of FH care

Importance of genetic counselling

- Counselling provides an ethical and psychosocial framework for informed decision-making before genetic testing

Tailored communication

- Genetic results communication must consider family's health literacy, culture, and psychological context

Shared decision-making process

- Testing involves informed agreement from guardians and assent or consent from the child when appropriate

Linking diagnosis to prevention

- Counselling highlights benefits of early diagnosis and starting LLT to reduce disease risk

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Screening strategies

Cascade screening efficiency

Cascade screening targets relatives of genetically confirmed FH cases, efficiently identifying high-risk families

Universal screening approach

Universal screening tests all children for elevated LDL-C, regardless of family history, enabling early detection

Opportunistic testing

Testing offered during healthcare visits for other conditions

Selective screening

Targeted testing of high-risk children (family history of premature ASCVD)

→ Paediatric FH screening can be implemented using different, complementary strategies.

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European experience & cost-effectiveness

Cascade-based programmes

- Netherlands: first national programme → highly cost-effective (>€8 return per €1 invested)
- Similar models: Norway, Czech Republic
- Cascade testing of children from adult probands in the UK

Universal / mixed models

- Slovenia: universal cholesterol screening at 5–6 years
- → genetic testing + cascade testing
- Germany (Bavaria): VRONI study
- Cost-effective in some countries (e.g., UK, Argentina but not US)

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Newborn screening

Potential of FH newborn screening

- Early FH detection at birth allows timely treatment, reducing cardiovascular risks for affected children and families

Genetic testing complexities

- Genetic tests detect uncertain variants, requiring cautious interpretation and follow-up to avoid misdiagnosis and anxiety

Challenges in diagnosis

- Variability in cholesterol levels at birth and infancy complicates reliable FH diagnosis using current biochemical markers

Future research needs

- Validated biomarkers and diagnostic pathways are essential to enable routine FH newborn screening and early prevention

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Rationale and updated recommendations for lowering LDL-C treatment goals in children with HeFH

New evidence

- Focus on reducing cumulative LDL-C burden (key driver of ASCVD)
- Early atherosclerosis begins in childhood
- Increased cIMT seen before age 10
- LLTs are safe & effective in children
- Early treatment → reduced cIMT & possible regression of lesions

Updated recommendations

Start treatment earlier
In the first decade of life, ideally from 6 years

New LDL-C targets:

- ≤3.5 mmol/L (135 mg/dL) at 6–<10 years
- ≤3.0 mmol/L (115 mg/dL) at 10 –<18 years (or with other major risk enhancers at 6–<10 years

Clinical considerations

- New LLTs approved from age 6 → enable earlier intervention
- Individualised treatment decisions (physician + family)
- Prioritise:
  Early initiation (before puberty)
  Long-term adherence

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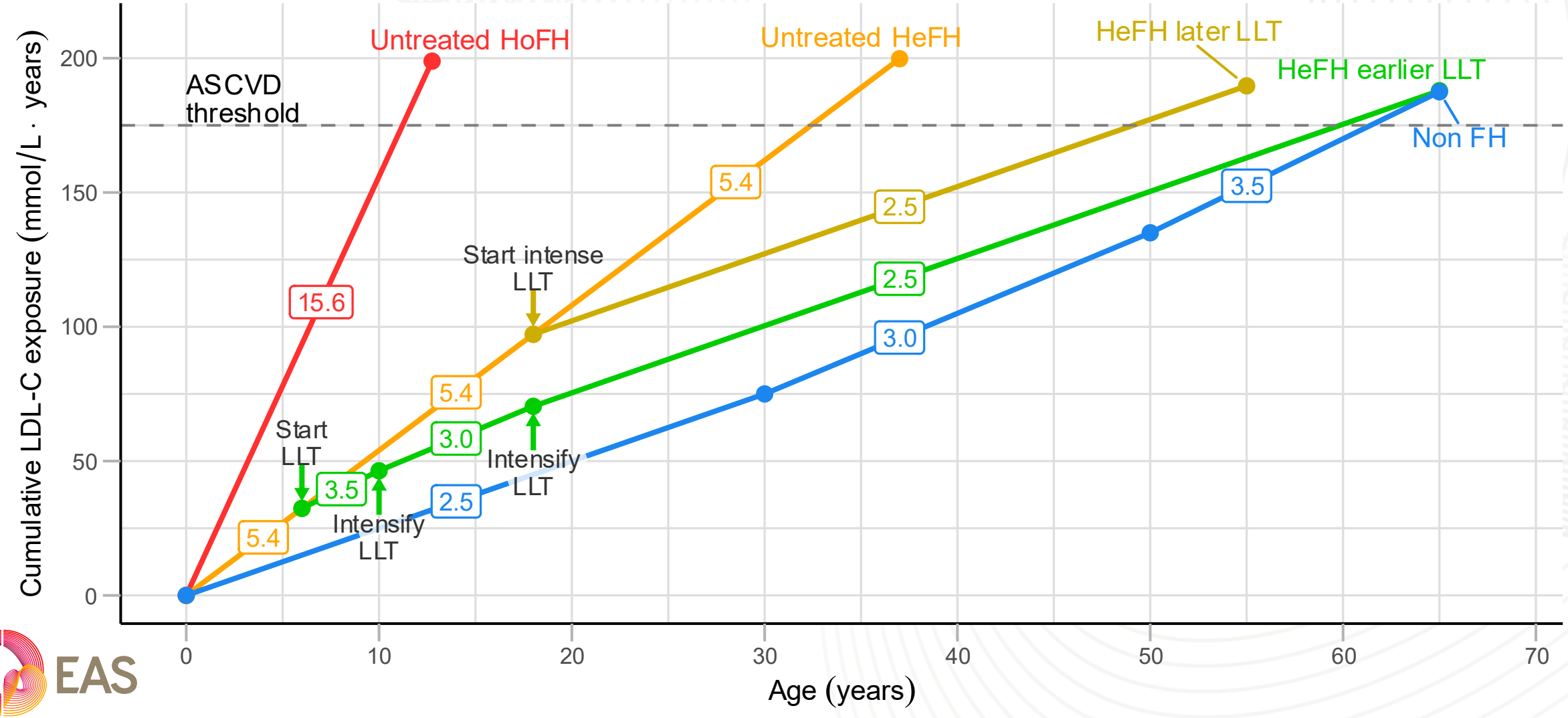
Cumulative LDL-C exposure in individuals with or without FH and the impact of starting LLT at 6 years or 18 years in HeFH



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Lifestyle measures

First-line approach

- Lifestyle measures are the first step, but usually insufficient alone
- Important even before pharmacological treatment
- May be sufficient in mild cases (LDL-C close to target)
- Supports adherence and sense of control

Core recommendations

- Encourage physical activity
- Avoid smoking, vaping, and obesity
- Treat other cardiovascular risk factors
- Promote family-based healthy diet

Nutritional goals

- ↓ LDL-C and overall cardiovascular risk
- Maintain normal growth and neurocognitive development

Dietary considerations

- Low-fat diet: safe (incl. STRIP study)
- Replace saturated fat → polyunsaturated fat

Risks to avoid

- Insufficient energy, essential fatty acids, vitamin E
- Development of eating disorders

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Table 2 Dietary components that should be limited or promoted in children with FH

Avoid or limit	
Dietary cholesterol	200-300 mg/day
Saturated and trans fatty acids: processed foods, animal fat, red meat, whole-fat dairy products, pastries, palm oil, and coconut oil	<7% Daily Energy Intake (DEI)
Added simple sugars, including fructose	<10% DEI
Promote	**Goals**
Balanced diet	Carbohydrate 45-60%, fat 25- 35%, protein 12-15% of DEI adapted to age
Structured complete and regular meals; stress importance of breakfast	
Low-fat dairy foods	
Long-chain polyunsaturated fatty acids (PUFA): oily fish twice a week, pulses, nuts, seeds, tofu, vegetable oils (rapeseed, soybean, corn, sunflower)	Promote n-3 PUFA; total PUFA 5-10% DEI
Monounsaturated fatty acids (MUFA): vegetable oils (rapeseed, olive, canola, peanut, sesame), avocados, nuts and seeds	10-15% DEI
Fibre: fresh fruits and vegetables, wholemeal bread, cereals, legumes	25-40 g/day, 7-13% soluble fibres
Intake of lean and fatty fish, shellfish, lean chicken and turkey (white meat, skinless), limited lean red meat (“>93% lean”, fat trimmed, free range)	

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Table 3 Approved lipid-lowering therapies for children with familial hypercholesterolaemia

Lipid-lowering therapy	Age approved/tested	Approved (or tested) dose range and route of administration	LDL-C reduction*	Key publications
Statins (HMG-CoA reductase inhibitors)				
Pitavastatin	≥6 years	1-4 mg (PO)	23-39% (placebo adjusted)	Braamskamp et al., 2015
Rosuvastatin	≥6 years	5-20 mg (PO)	35-45%	Braamskamp et al., 2015 Stein et al., 2017 (HoFH)
Pravastatin	≥8 years	20-40 mg (PO)	24% (placebo adjusted)	Wiegman et al., 2004
Atorvastatin	≥10 years	10-20 mg (PO)	40% (placebo adjusted)	McCrindle et al., 2003 Raal et al., 2000 (HoFH)
Fluvastatin	≥10 years	20-80 mg (PO)	34%	van der Graaf et al., 2006
Lovastatin	≥10 years	10-40 mg (PO)	17-27% (placebo adjusted)	Stein et al., 1999 (in boys) Clauss et al., 2005 (in girls)
Simvastatin	≥10 years	10-40 mg (PO)	31-40% (placebo adjusted)	de Jongh et al., 2002
Inhibitor of intestinal cholesterol absorption				
Ezetimibe	≥6 years EMA ≥10 years FDA	10 mg (PO)	27% as monotherapy (placebo adjusted) 15% on top of simvastatin (placebo adjusted)	Kusters et al., 2015 Van der Graaf et al., 2008

Table 3 Approved lipid-lowering therapies for children with familial hypercholesterolaemia (*continued*)

PCSK9 inhibitors				
Alirocumab	≥8 years (not approved for HoFH <18 years)	If <50 kg: 150 mg (SC) q4w and 40 mg (SC) q2W If ≥ 50 kg: 300 mg (SC) q4w and 75 mg (SC) q2W	34-43% on top of background LLT (placebo adjusted)	Santos et al., 2024
Evolocumab	≥10 years	420 mg (SC) q4w and 140 mg (SC) q2w	38% on top of background LLT (placebo adjusted)	Santos et al., 2020 Santos et al., 2022 Raal et al., 2024 (HoFH)
Inclisiran	≥12 years**	300 mg (SC) at 0 and 90 days and then q6m	29-34% on top of background LLT (placebo adjusted)	Wiegman et al., 2026 Wiegman et al., 2025 (HoFH)
Bile acid sequestrant				
Colesevelam	10 years (avoid in HeFH***)	1.875-3.75 g (PO)	6-12% (placebo adjusted)	Stein et al., 2010
ANGPTL3 inhibitor				
Evinacumab	≥6 months EMA ≥1 year FDA (approved for HoFH)	15 mg/kg (IV) q4w	48%	Wiegman et al., 2024 (HoFH)
Microsomal triglyceride transfer protein inhibitor				
Lomitapide	≥2 years** (approved for HoFH)	2-60 mg based on age, weight and tolerability (PO)	53%	Masana et al., 2024 (HoFH)

Sex differences

- **Men:** higher risk of premature ASCVD

- **Women:** higher cumulative LDL-C burden from early life
- Higher LDL-C levels already in childhood
- Treatment interruptions due to:
  – family planning
  – pregnancy
  – breastfeeding
  → ~2.3 years off-treatment

→ Results in greater lifetime LDL-C exposure in women
→ Start treatment equally early and maintain continuity in girls and boys

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Safety

Statins

- Well tolerated
- Rare creatine kinase / hepatic aminotransferases elevations
- No insulin changes in children

Other therapies

- Ezetimibe: well tolerated
- Bile acid sequestrants: gastrointestinal side effects

PCSK9 inhibitors

- Injection site reactions
- No impact on growth, puberty, cognition
- Long-term data limited

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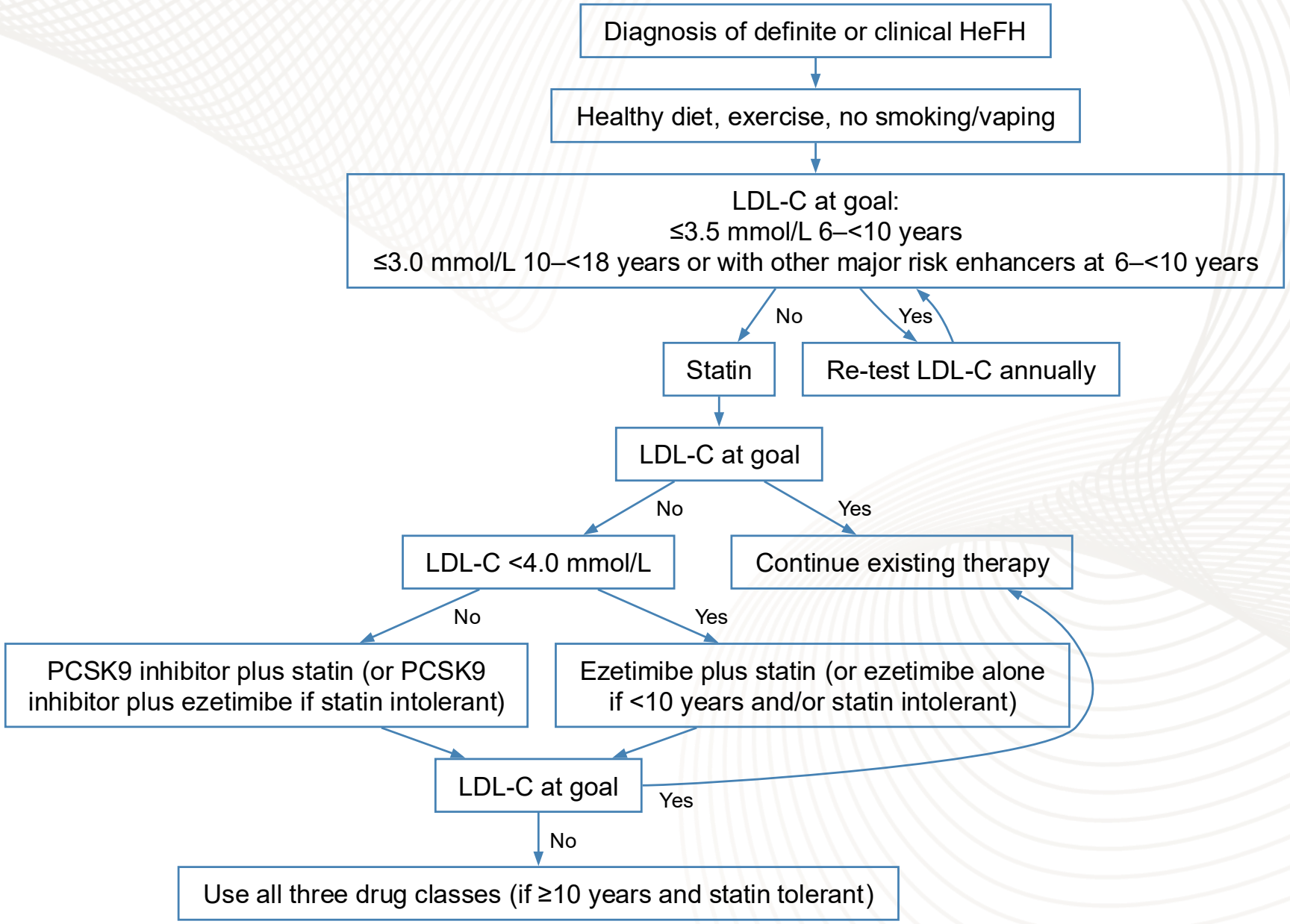
Treatment algorithm for children with HeFH



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Clinical management of HoFH

Clinical recognition

- LDL-C >10 mmol/L (>400 mg/dL)
- Xanthomas before age 10
- Early atherosclerosis:
  - aortic root
  - coronary ostia
  - aortic valves

Can develop within first 2 decades

Aortic disease may progress even with LDL-C reduction

→ **Start treatment immediately after diagnosis**

Early detection & genetics

- Test high-risk children early (newborn–2 years)
- LDL-C measurement + genetic confirmation
- Consider family history (both parents FH)

- HoFH = biallelic pathogenic variants
- Genes: *LDLR*, *APOB*, *PCSK9*, *LDLRAP1*
  Includes:
- Monogenic (same gene)
- Compound heterozygous
- Digenic forms

→ **Clear classification is essential for treatment access**

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Management of HoFH in children

Cardiovascular imaging	LDL-C treatment goals	Treatment strategy
• Screen for subclinical ASCVD + aortic valve disease • CCTA ≥3 years, then as clinically indicated • Guides treatment intensity and follow-up Advanced imaging (e.g. photon-counting CT) → improved plaque characterization	• ≤3.0 mmol/L (115 mg/dL) from diagnosis • Prevents plaque progression If ASCVD: • ≤1.8 mmol/L (70 mg/dL) **Time-weighted LDL exposure matters**	Lifestyle + statin + ezetimibe ↓ Assess LDL-C after a few weeks ↓ If not at goal & residual LDLR: → add PCSK9 inhibitor ↓ If no LDLR activity / insufficient response: → consider LDLR-independent therapies

Early imaging + aggressive LDL-C lowering + tailored therapy = improved outcomes

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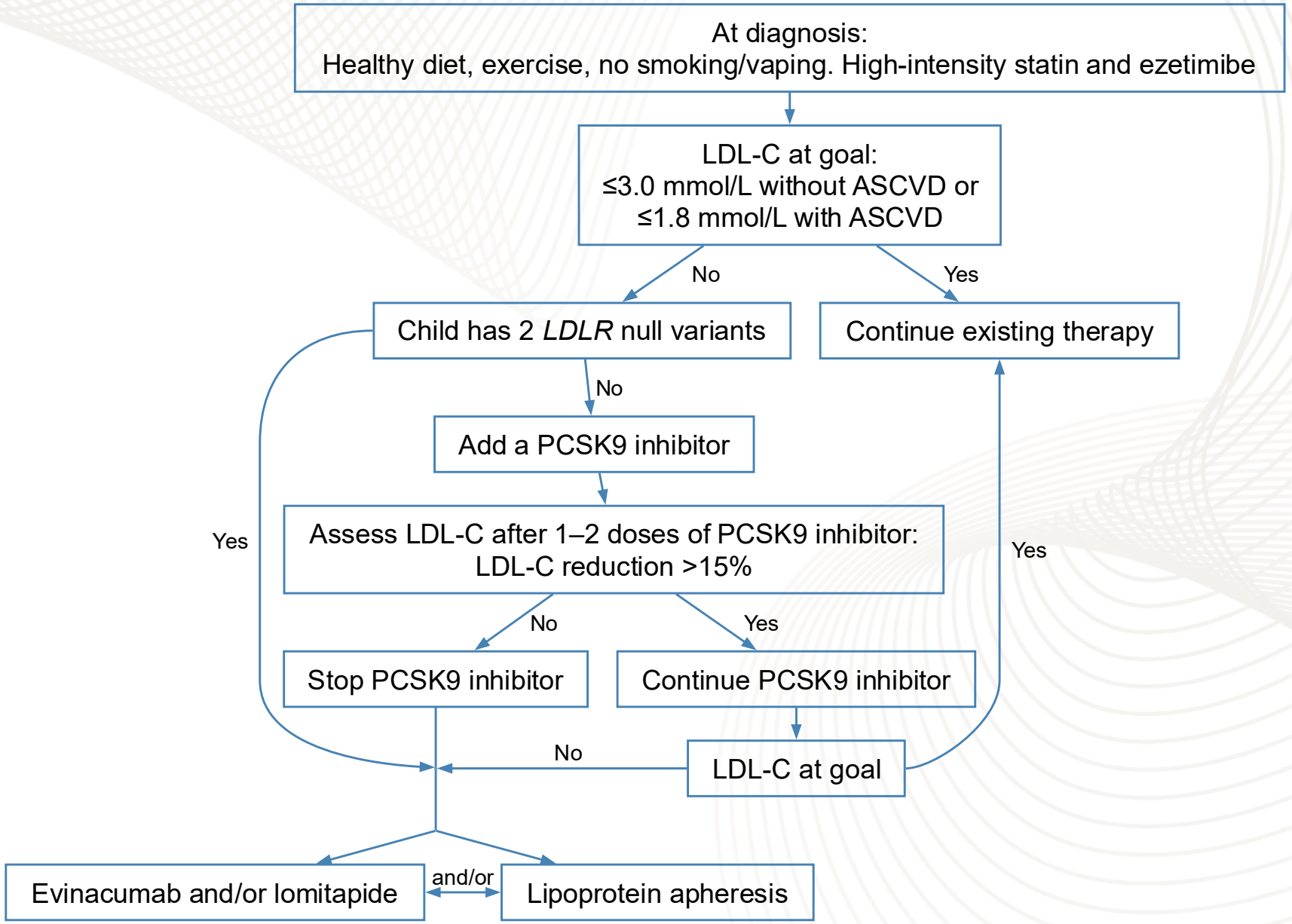
Treatment algorithm for children with HoFH



LDLR-independent therapies in HoFH

Evinacumab

- Monoclonal antibody targeting ANGPTL3 → ↓ LDL-C independent of LDLR
- ~48% LDL-C reduction (children 5–11 yrs, 24 weeks)
- Plaque reduction up to 76–85% (case data)

Use:

- Approved (EMA/FDA) from 6–12 months
- Effective in LDLR null/null patients

Lomitapide

- MTP inhibitor → ↓ VLDL/LDL production
- ~50% LDL-C reduction

Use:

- Approved from ≥2 years (FDA)
- Effective in children (5–17 yrs)

Considerations:

- Hepatic & gastrointestinal side effects
- Requires low-fat diet

LDLR-independent therapies enable **effective LDL-C reduction even without LDLR activity**

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Lipoprotein apheresis

Lipoprotein apheresis in HoFH

- LDLR-independent therapy (from age 2–3 years)
- Removes LDL-C, ApoB, Lp(a); reduces inflammation
- Every 1–2 weeks (2–3 hours/session)
- LDL-C reduction: ~75% acute, ~48% chronic
- LDL-C rebounds → repeated treatment needed

Clinical use

- Add if LDL-C targets not achieved with drugs
- Combine with evinacumab in severe cases
- Limitations: time, cost, access, quality of life impact
- Alternative: plasma exchange
- Liver transplantation in exceptional cases

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Transition to an adult model of healthecare

Childhood	Adolescence	Young adult
Early education	**Transition phase**	**Adult care**
• Start ≤10 years • Build understanding of FH • Introduce treatment & lifestyle	• Risk of low adherence • Competing priorities • Develop self-management skills	• Independent healthcare use • Maintain follow-up • Recognise cardiac symptoms

Higher risk in HoFH & severe HeFH
→ Know symptoms & seek urgent care

Early education + structured transition → better lifelong adherence and outcomes

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Proposals to facilitate a smooth transition to an adult model of healthcare for FH

1. Children with FH should be taught about their condition and its management as early as possible, and definitely by the age of 10 years.

2. The importance of diet, healthy lifestyle measures and avoidance of smoking/vaping should be explained and stressed before puberty

3. Adherence to LLT should be monitored, especially during puberty

4. Girls should be given advice on contraception

5. If adolescents wish, they can be seen (partly) without their parents

6. Before transfer to the adult service, adolescents should be made aware that from age 18: (i) LLTs other than those used in childhood are approved and prescribed; and (ii) LDL-C treatment goals will be lowered to 1.8 mmol/L (70 mg/dL)

7. Upon transfer to the adult service, the hospital physician taking over care from the paediatrician should actively review and, if necessary, adjust the lipid-lowering regimen. This should be clearly emphasized during the handover of care

8. If other major risk enhancers are present, one could strive from age 16 for a lower LDL-C goal to facilitate transition to adulthood when the treatment goal will be lowered to LDL-C <1.4 mmol/L (55 mg/dL) according to the 2025 update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias

9. An adolescent with FH, and especially those with HoFH, should preferably attend a transition clinic or a joint clinic with the paediatrician and internist/cardiologist at least once before transfer to the adult service

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Improving implementation of FH care

Challenge	Key strategies	System-level actions
• Gap between evidence and practice • Need for structured implementation models → implementation → operationalization → evaluation	• Personalized & transitional care plans • Shared decision-making (culturally appropriate) • Tools to improve communication & adherence • Multidisciplinary care + family medicine • Digital tools & clinician support	• Share resources & expertise across centres • Use registry data & advocacy to influence policy • Secure government funding → enable centres of excellence → access to new therapies

Implementation-focused care models are essential to improve outcomes in children with FH

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Box 4 Proposals for future studies in paediatric FH

- Establish thresholds in imaging for excessive subclinical atherosclerosis
- Cost-effectiveness studies to compare screening strategies
- Develop more reliable tools to be used for newborn screening
- Include FH in genomic newborn screening studies
- Demonstrate the benefit of polygenic risk scores in children
- Investigate the effectiveness of a cholesterol-lowering diet on ASCVD incidence and mortality
- Examine the combined risk of FH and elevated Lp(a) in childhood

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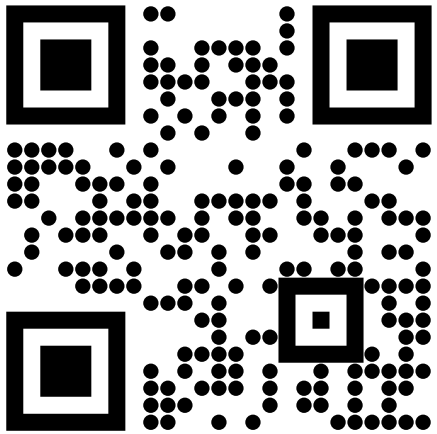

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