In the name of God

Case Presentation

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Patient ID:

- Gender: woman
- Age: 8-year-old
- Source of History: Mother, Reliable
- NotMarried
- Born & live in Tehran
- Education: Student

Chief complaint:

- Skin Lesion from birth
- Refer for LDL-C evaluation
- Candidate for liver transplantation

Present illness:

- At the birth she had a skin lesion in the back
- At age 4 skin lesions increased in different part of her body
- lipid profil test at age 4 showed hypercholesterolemia
- She was initially treated with statin 10 then 20 and 40mg
- After 2 months ezetimibe 10mg and then fenofibrate is added

Biochemistry Dpt.

B.U.N		7	mg/dl	7 - 20
Creatinine		0.4	mg/dl	0.3 - 0.6
Cholesterol	✓	907	mg/dl	Desirable < 200 Borderline high c High chol: >240
Triglyceride	H	165	mg/dl	32 - 116
HDL	✓ L	19	mg/dl	45 - 65
LDL	✓ H	793	mg/dl	57 - 130
VLDL		95	mg/dl	5 - 40
LDL/HDL Ratio		41.7		Ratio > 3 increase atherosclerosis
Calcium		9.7	mg/dl	8.5 - 10.5
S.G.O.T (AST)		23	IU/L	0 - 31
S.G.P.T(ALT)		11	IU/L	5 - 33

Comments : The results has been checked, indicate possible familial hypercholeste

Che

Hormone Dpt.

T4 (CLIA)	10.1	ug/dL	5.5 - 12.1
TSH (CLIA)	1.81	uIU/mL	0.70 - 4.80
25-Hydroxy Vitamin D (CLIA)	13.0	ng/ml	Deficient : <

PMHx

- Born from s/c in term
- B.W=3.860
- Admit in neonate for jaundice 40 days
- Her growth &development was normal

FMHx

- Mother & father are cousin
- she has one brother .his BMI =32.2
- maternal grandfather was died at 42 suddenly
- Her aunts have hyper lipidemia
- Her uncle is esrd

Mother`s lab

- BMI= 32.7
- Chol=307
- LDL-C=182
- HDL-C=68
- T.G=283

Father`s Lab

- BMI=21.7
- CHOL=281
- LDL=201
- HDL=58
- T.G=111

brother`s lab

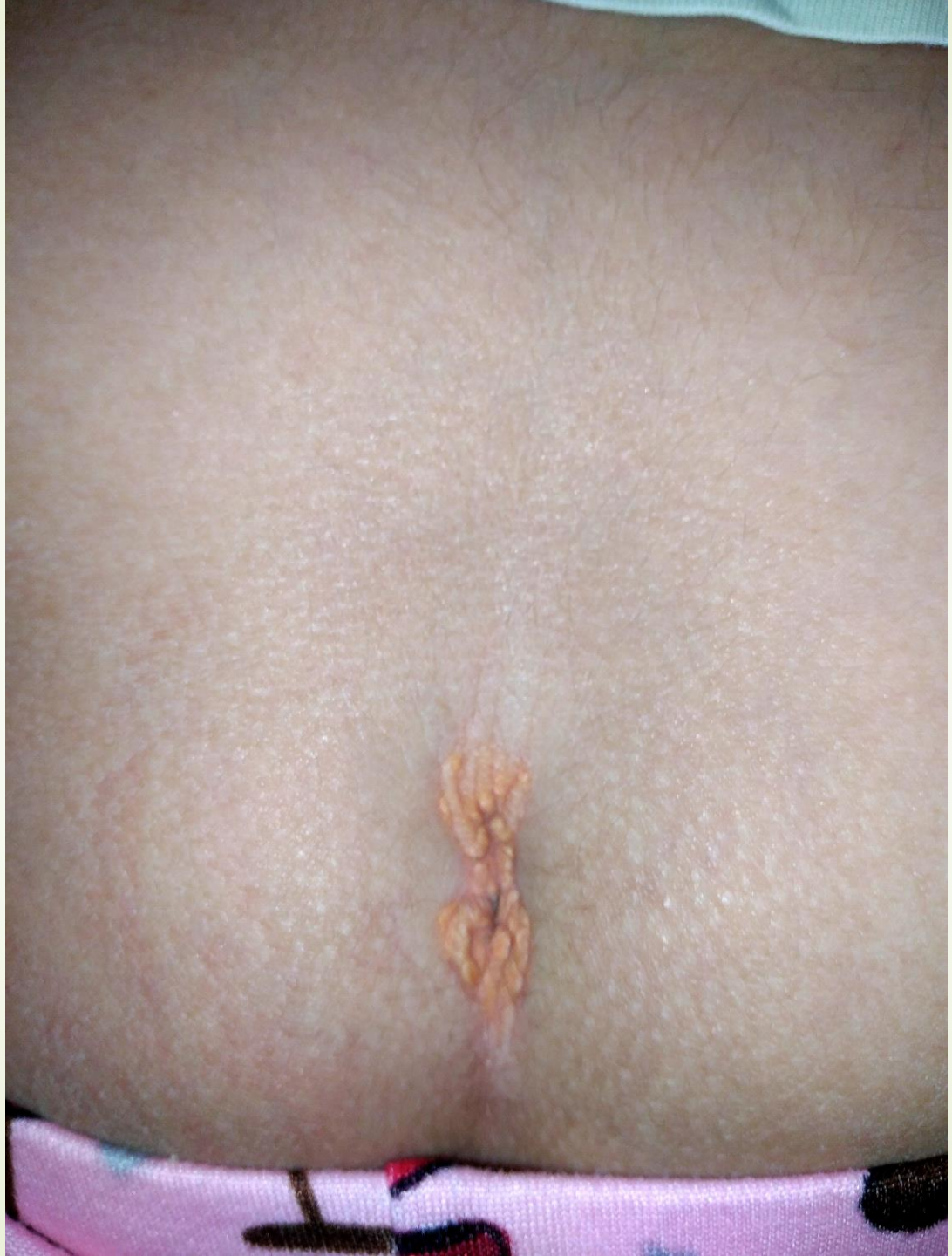
BMI=32.2

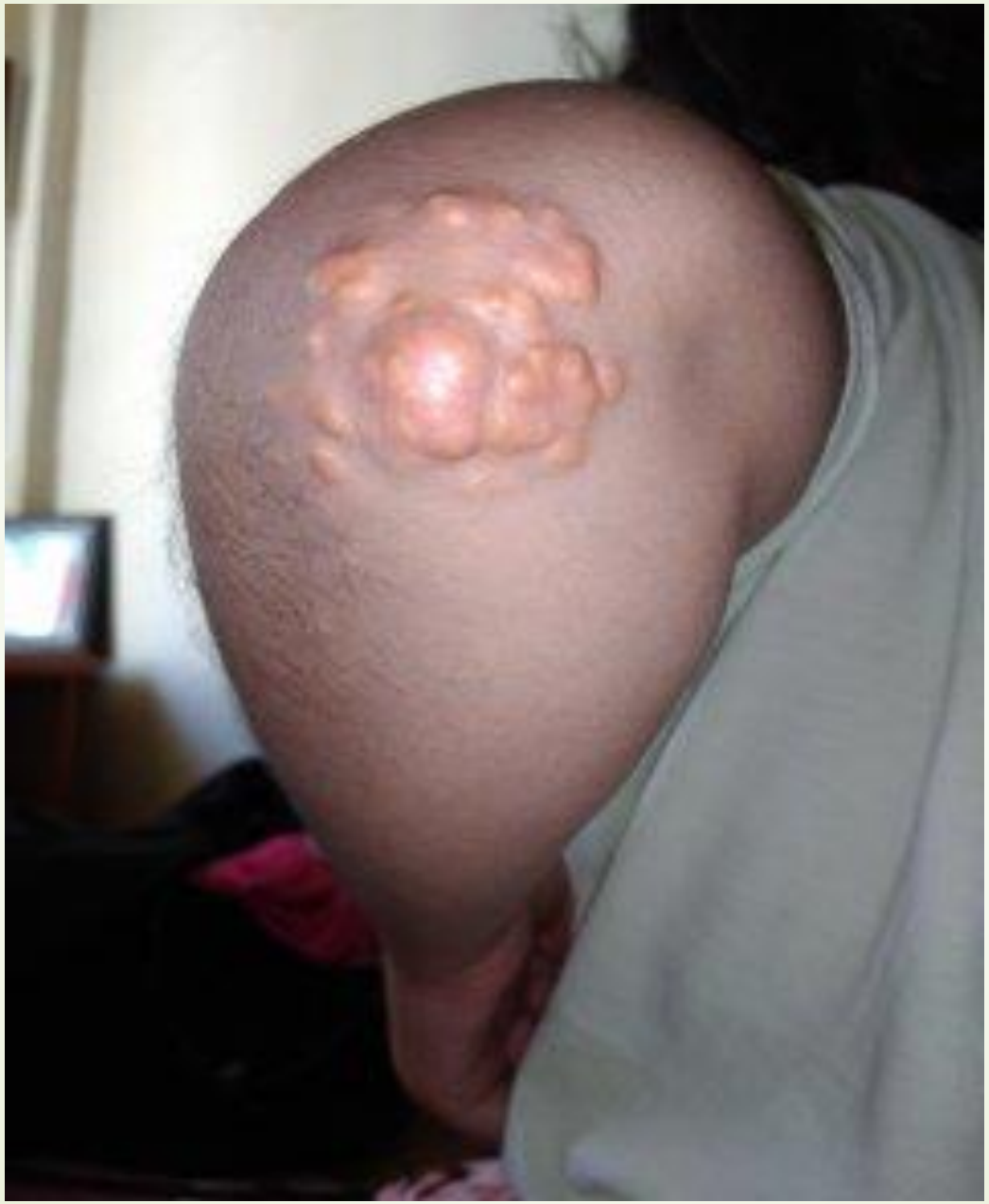
CHOL=217

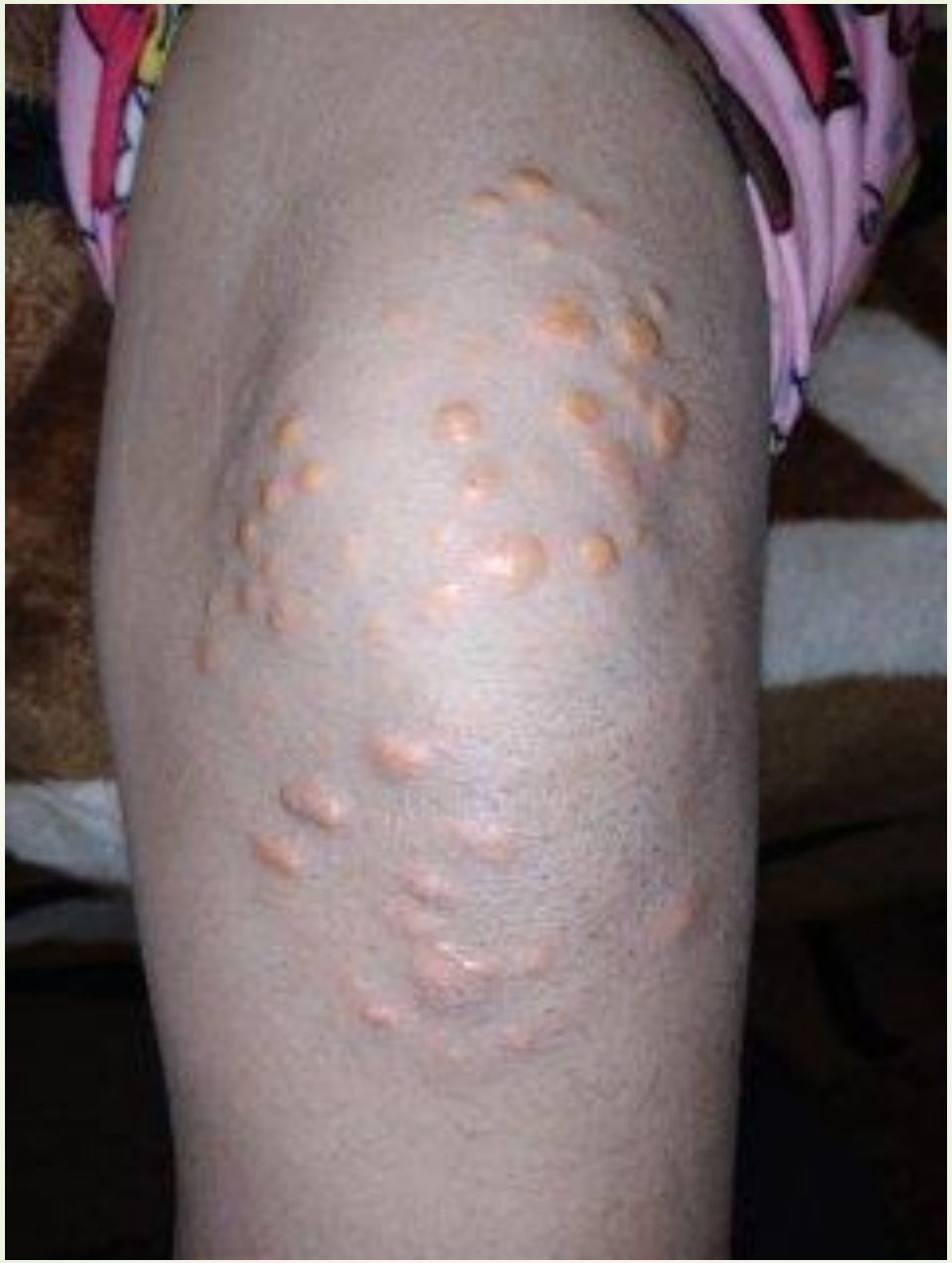
LDL-C=137

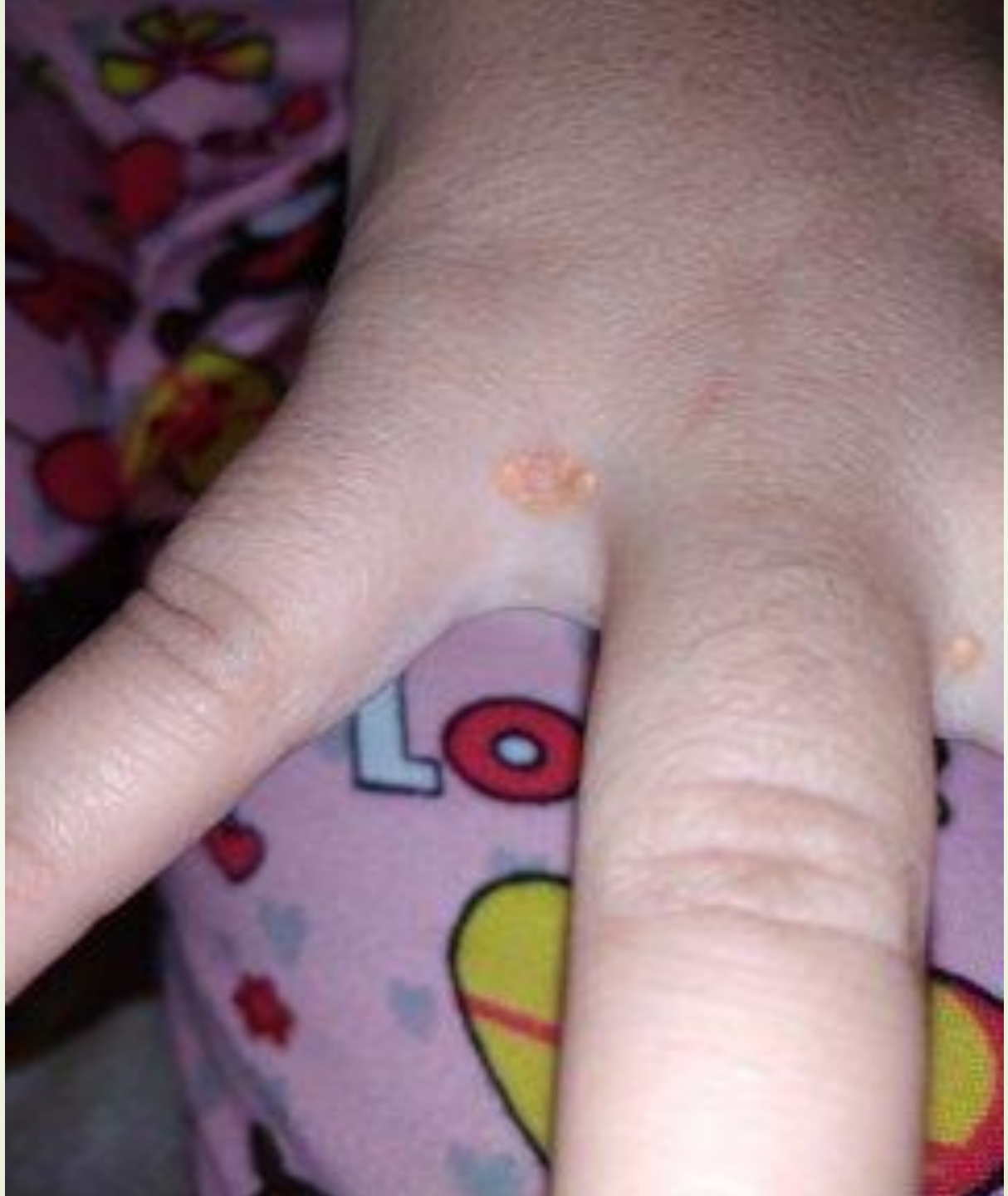
HDL-C=48

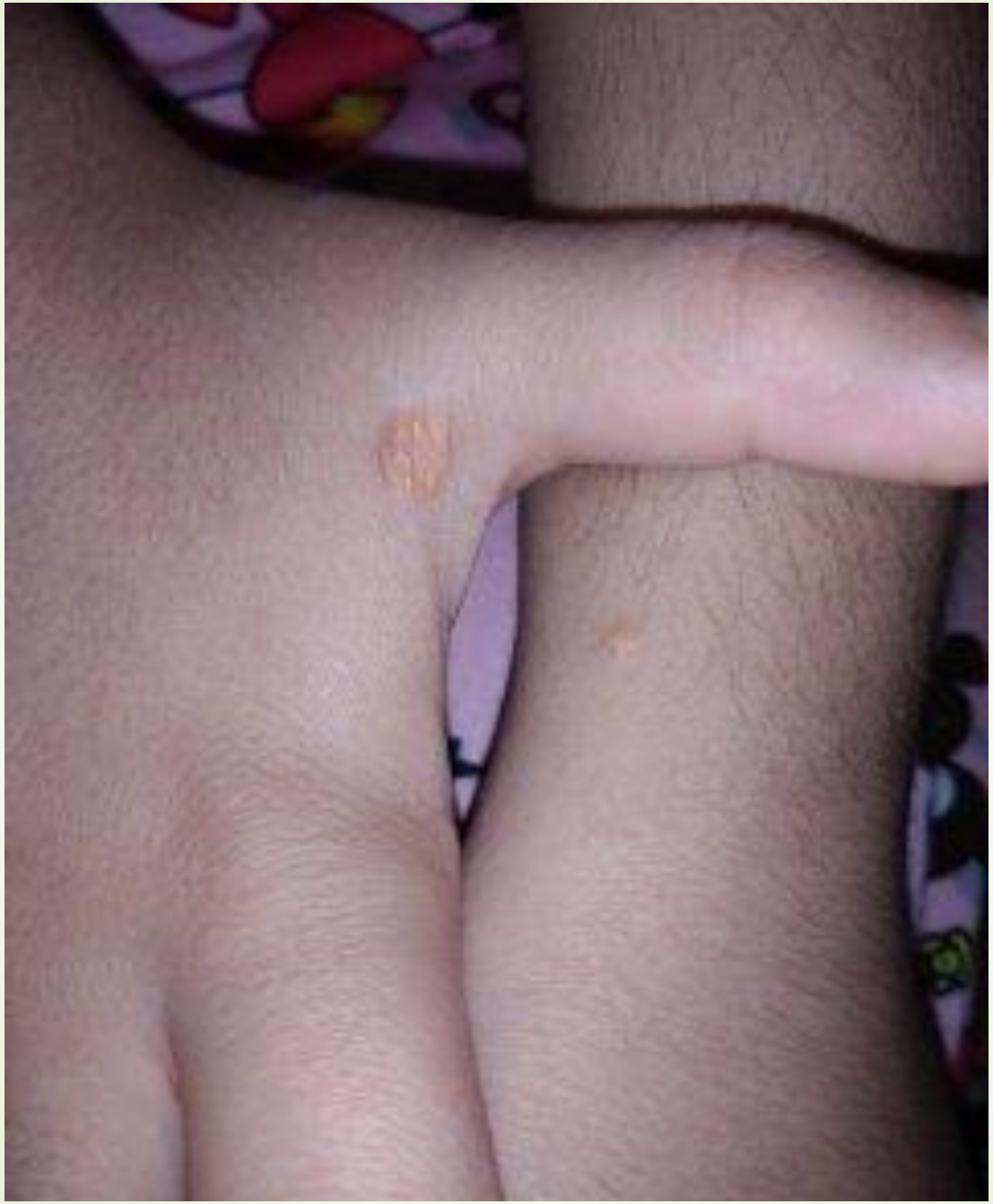
TG=161











Lipid profil under treatment of statin, ezetimab & clofibrate

	شهریور 98	دی 98	اردیبهشت 99	ابان99	مرداد 1400	ابان 1400	شهریور 1401
CHOL	907	788	840	829	809	698	750
LDL-C	793	667	606	464	729	616	666
HDL-C	19	97	99	94	43	55	50
T.G	165	119			184	134	170

The patient treated with PCSK9I at mehr 1402

	مرداد 1402 Before evolocomab	مهر 1402 AFTER EVOLOCOMAB	آبان 1402 AFTER EVOLOCOMAB
2CHOL	766	797	805
LDL-C	674	506	702
HDL-C	59	63	70
T.G	164	139	165
	AST=43 ALT=56 ALP=266		AST=68 ALT=159 ALP=510

nature reviews cardiology

https://doi.org/10.1038/s41569-023-00892-0

Evidence-based guidelines

Check for updates

International Atherosclerosis Society guidance for implementing best practice in the care of familial hypercholesterolaemia

Gerald F. Watts[1,2] ✉, Samuel S. Gidding[3], Robert A. Hegele[4], Frederick J. Raal[5], Amy C. Sturm[3,6], Laney K. Jones[3], Mitchell N. Sarkies[7], Khalid Al-Rasadi[8], Dirk J. Blom[9], Magdalena Daccord[10], Sarah D. de Ferranti[11], Emanuela Folco[12], Peter Libby[13], Pedro Mata[14], Hapizah M. Nawawi[15,16], Uma Ramaswami[17], Kausik K. Ray[18], Claudia Stefanutti[19], Shizuya Yamashita[20], Jing Pang[1], Gilbert R. Thompson[21] & Raul D. Santos[22,23]

Abstract

Sections

- FH is an overall phenotypic frequency in the population of 1 in 311
- FH may affect up to 35 million people worldwide, but only 10% are currently diagnosed

Table 1 | Clinical recommendations on screening for familial hypercholesterolaemia

Clinical recommendations	Class	Level
1. Multiple screening strategies (for example, selective, opportunistic and/or universal) should ideally be used to detect index cases with FH	1	B
2. Age-specific, sex-specific and country-specific LDL-cholesterol concentrations (estimated in plasma or serum) above the corresponding 95th percentiles for the population should preferably be used to screen for index cases with FH	1	B
3. Selective screening should be used to detect index cases among adults with premature ASCVD, mainly coronary artery disease, and a family history of premature ASCVD and/or hypercholesterolaemia	1	A
4. Opportunistic screening, such as an LDL-cholesterol concentration >4.9 mmol/l (≥190 mg/dl), should be used to detect cases in the community	1	B
5. Universal screening using age-specific and sex-specific criteria for LDL-cholesterol concentration should be considered initially to detect children and adolescents with FH, after which the diagnosis should be formally confirmed and reverse cascade testing offered to parents, as indicated	2	B
6. Cascade testing should be offered to all close relatives of an index case with definite FH and be carried out using phenotypic and genetic methods; if genetic testing is not feasible, LDL-cholesterol testing (based on appropriate age-specific and gender-specific thresholds) should be used	1	A
7. Genome-based population screening of adults may be considered for wider and more accurate detection of FH, but requires careful implementation	3	C
8. After initial detection of potential index cases, the diagnosis of FH should be formally confirmed using country-specific (or internationally accepted) phenotypic criteria and ideally with genetic testing	1	A
9. Children with suspected HoFH (for example, with physical stigmata), or at risk of FH (both parents known to have FH), should be tested as early as possible (at the newborn stage or by 2 years of age), with measurement of LDL-cholesterol concentrations, followed by genetic confirmation	1	B
10. Screening of children at risk of HeFH should be considered using LDL-cholesterol concentrations at or after the age of 5 years, or as early as 2 years in those with a strong family history of premature ASCVD, with confirmation of the diagnosis genetically, as indicated	2	B
11. Non-fasting samples may be considered when screening for FH; the Friedewald equation should be used with caution owing to the confounding effect of hypertriglyceridaemia on the estimation of LDL-cholesterol concentration	3	B
12. Patients with hypertriglyceridaemia > 4.5 mmol/l (>400 mg/dl), in whom FH is strongly suspected, should be re-screened for FH with a 12-h fasting sample and LDL-cholesterol concentration measured using a direct assay	1	A
13. In the absence of a direct assay for LDL-cholesterol concentration, the probability of FH should be reconsidered in patients with very severe hypertriglyceridaemia after therapeutic lowering of triglyceride concentrations to <4.5 mmol/l (<400 mg/dl), or by calculating LDL-cholesterol using a novel equation, if triglycerides are between 4.5 mmol/l and 10.0 mmol/l (400–850 mg/dl)	2	C
14. The effects of cholesterol-lowering medications and acute illness should be accounted for when phenotypically screening for FH; LDL-cholesterol concentrations should be adjusted for the use of statins, ezetimibe, PCSK9 inhibitors and other therapies, particularly if a reliable pretreatment value is unavailable; if the diagnosis of FH is in doubt, LDL-cholesterol measurement should be repeated after full recovery from acute illness	1	B

ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia; PCSK9, proprotein convertase subtilisin/kexin type 9.

screening

- LDL-cholesterol concentrations above 95th percentiles for the population should preferably be used to screen for index cases with FH
- Selective screening among adults with
  - a premature ASCVD,
  - family history of premature ASCVD and/or hypercholesterolaemi

screening

- Children with suspected HoFH (
- , with physical stigmata)
- , or at risk of FH (both parents known to have FH),
- should be tested as early as possible (at the newborn stage or by 2 years of age),
- followed by genetic confirmation

screening

- . Screening of children at risk of HeFH
  - LDL-c concentrations at or after the age of 5 years
  - 2 years in those with a strong family history of premature ASCVD

Table 2 | Clinical recommendations on diagnosis of familial hypercholesterolaemia

Clinical recommendations	Class	Level
1. A diagnosis of HeFH or HoFH should be made, whenever possible, using genetic testing that identifies pathogenic variants (such as in *LDLR*, *APOB*, *PCSK9* or *LDLRAP1*) that impair the LDL-receptor pathway; such testing is particularly important when phenotypic features are less obvious, such as in children, and for planning long-term care and cascade testing of family members. Conversely, if the phenotype strongly suggests FH and a pathogenic or likely pathogenic variant is not detected, FH should not be excluded	1	A
2. If genetic testing is not feasible, a clinical diagnosis of FH in adults should be made using country-specific or recognized phenotypic criteria (such as the Dutch Lipid Clinic Network, Simon Broome criteria, MED-PED, AHA, Canadian or Japanese criteria) for index cases (Supplementary Material 2)	1	A
3. A phenotypic diagnosis of FH in adults and children requires exclusion of, or correction for secondary causes of, high LDL-cholesterol concentrations (Supplementary Material 3); in the absence of an untreated value, LDL-cholesterol concentration should be adjusted for concurrent use of cholesterol-lowering medication; LDL-cholesterol concentrations should ideally be measured after fasting and on two occasions	1	A
4. Use of imaging-based detection of subclinical Achilles tendon xanthomas may be considered to increase the specificity and accuracy of the phenotypic diagnosis of FH in adults	3	B
5. A clinical diagnosis of FH in children and adolescents should be considered as highly probable in the presence of an untreated LDL-cholesterol concentration >4.9 mmol/l (>190 mg/dl), recorded on at least two occasions (fasting lipid profile, >2 weeks but <3 months apart), and a parental history of high LDL-cholesterol levels, premature ASCVD or a positive genetic test for FH	2	B
6. After exclusion of secondary causes of high LDL-cholesterol levels (Supplementary Material 3), a clinical diagnosis of FH in children and adolescents should be considered as probable in the presence of an untreated (a) LDL-cholesterol concentration > 4.9 mmol/l (>190 mg/dl; recorded on at least two occasions), even in the absence of a parental history of high LDL-cholesterol concentrations or premature ASCVD; (b) LDL-cholesterol concentration > 4.0 mmol/l (>160 mg/dl; recorded on at least two occasions), with a parental history of high LDL-cholesterol concentrations or premature ASCVD; (c) LDL-cholesterol concentration > 3.5 mmol/l (>135 mg/dl; recorded on at least two occasions), with a parent having a pathogenic gene variant for FH; (d) LDL-cholesterol concentration (recorded on at least two occasions) exceeding a country-specific LDL-cholesterol threshold (lower than the above) and a parental history of elevated LDL-cholesterol concentrations or premature ASCVD	2	B
7. Phenotypic criteria developed for making a diagnosis of HeFH in adult index cases (such as the Dutch Lipid Clinic Network criteria) should not be used in children or adolescents, or when undertaking cascade testing	1	A
8. After excluding secondary causes of high LDL-cholesterol levels (Supplementary Material 3), a clinical diagnosis of HoFH (that is, phenotypic HoFH) should be made in children and adults with an untreated LDL-cholesterol concentration > 10 mmol/l (>400 mg/dl; recorded on two occasions) in the presence of (a) physical stigmata (tendon or cutaneous xanthomas, arcus cornealis) before the age of 10 years and/or (b) untreated LDL-cholesterol concentrations consistent with HeFH in both parents; in the absence of genetic testing and a clear history of FH in both parents, sitosterolaemia and hypercholesterolaemia (cerebrotendinous xanthomatosis) should also be excluded	1	C
9. If cascade testing in the family is recommended, the diagnosis of FH in the proband or index case should ideally be confirmed genetically	1	A
10. The diagnosis of FH during phenotypic cascade testing should be made using age-specific, sex-specific and country-specific LDL-cholesterol concentrations, ideally measured after fasting and on two occasions	1	A

ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia;

Diagnosis

- The most accurate way to diagnose FH is by genetic testing
  - expensive
  - not universally available
  - may not capture all pathogenic variants
- Diagnosis of FH often relies on phenotypic criteria alone

diagnosis of FH

- A diagnosis of HeFH or HoFH should be made, whenever possible, using genetic testing
- If genetic testing is not feasible, a clinical diagnosis of FH in adults should be made using recognized phenotypic criteria
- A phenotypic diagnosis of FH requires exclusion of, or correction for secondary causes of, high LDL-cholesterol

Criteria	Points
Family history	
First-degree relative with known premature* coronary and vascular disease, OR	1
First-degree relative with known LDL-C level above the 95th percentile	
First-degree relative with tendinous xanthomata and/or arcus cornealis, OR	2
Children aged less than 18 years with LDL-C level above the 95th percentile	
Clinical history	
Patient with premature* coronary artery disease	2
Patient with premature* cerebral or peripheral vascular disease	1
Physical examination	
Tendinous xanthomata	6
Arcus cornealis prior to age 45 years	4
Cholesterol levels mg/dL mg/dL (mmol/L)	
LDL-C >= 330 mg/dL (≥8.5)	8
LDL-C 250 – 329 mg/dL (6.5–8.4)	5
LDL-C 190 – 249 mg/dL (5.0–6.4)	3
LDL-C 155 – 189 mg/dL (4.0–4.9)	1
DNA analysis	
Functional mutation in the LDLR, apo B or PCSK9 gene	8
Diagnosis (diagnosis is based on the total number of points obtained)	
Definite familial hypercholesterolemia	>8
Probable familial hypercholesterolemia	6–8
Possible familial hypercholesterolemia	3–5
Unlikely familial hypercholesterolemia	<3

*Premature = <55 years in men; <60 years in women.
Apo B: Apolipoprotein B; FH: Familial hypercholesterolemia; LDL-C: Low-density lipoprotein cholesterol; LDLR: Low-density lipoprotein receptor; PCSK9: Proprotein convertase subtilisin/kexin type 9.

Table 4. Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolemia

diagnosis of FH in children and adolescents highly probable

- LDL-c>190 mg/dl
- parental history of high LDL-c
- , premature ASCVD
- or a positive genetic test for FH

a clinical diagnosis of FH in children and adolescents probable

- LDL-cholesterol >190 mg/dl; even in the absence of a parental high LDL-c or premature ASCVD
- LDL-c >160 mg/dl; with a parental history of high LDL or premature ASCVD
- LDL-c>135 mg/dl; with a parent having a pathogenic gene variant for FH

clinical diagnosis of phenotypic HoFH children and adults

- LDL-c >400 mg/dl
- physical stigmata tendon or cutaneous xanthomas, arcus cornealis
- LDL-c consistent with HeFH in both parents;

Evidence-based guidelines

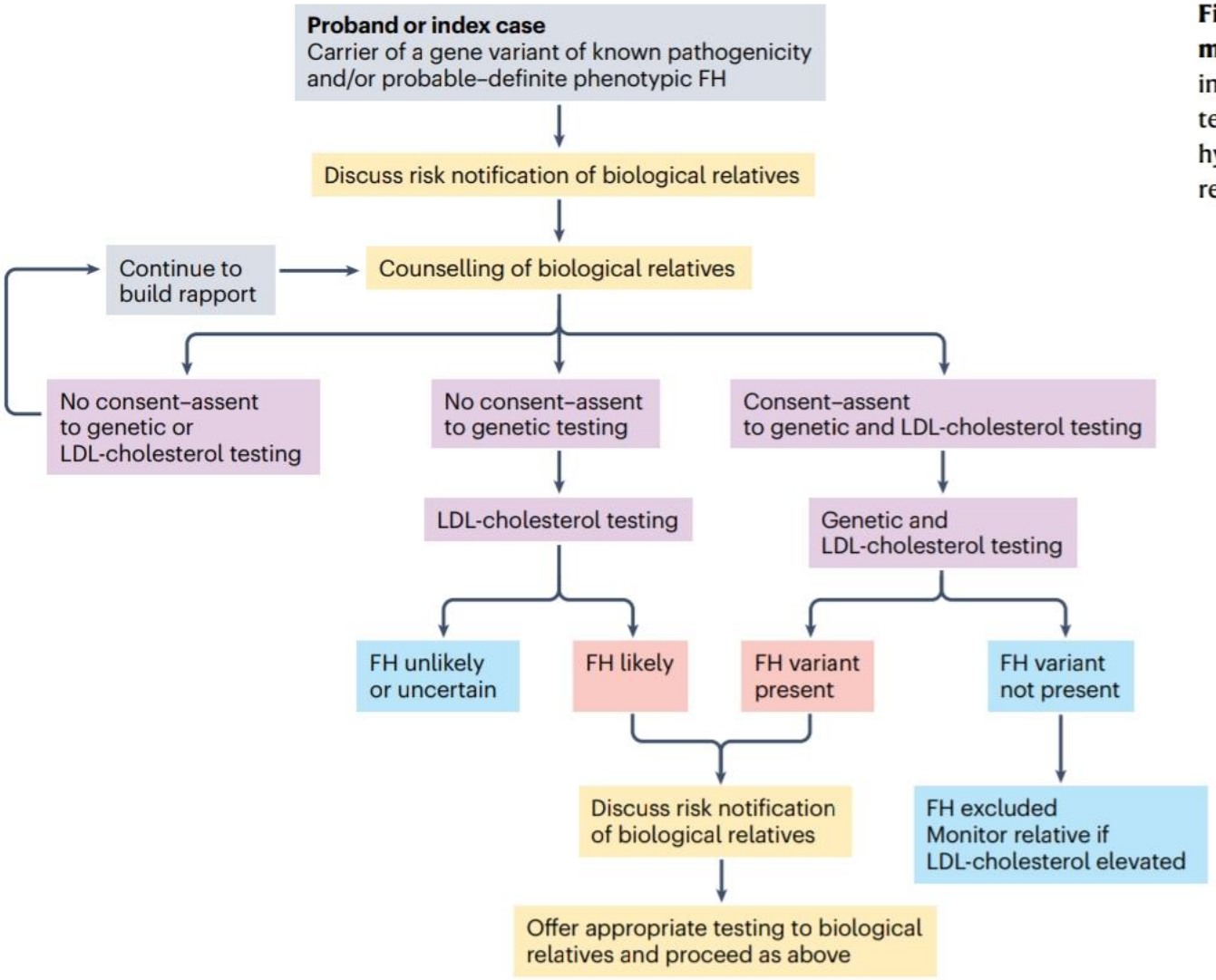


Fig. 1 | Algorithm for cascade testing of family members for familial hypercholesterolaemia. Options include using LDL-cholesterol testing alone or genetic testing together with LDL-cholesterol testing. FH, familial hypercholesterolaemia. Adapted with permission from ref. 17, Elsevier.

Table 3 | Clinical recommendations on genetic testing and counselling for familial hypercholesterolaemia

Clinical recommendations	Class	Level
1. Genetic testing for FH should be offered to all individuals in whom there is a strong suspicion of FH based on clinical and/or family history (for example, phenotypic HoFH, definite or highly probable phenotypic HeFH in an adult, child or adolescent)	1	B
2. Genetic testing should be considered in individuals with a probable phenotypic diagnosis of HeFH	2	B
3. Genetic testing may be considered in individuals with a phenotypic diagnosis of possible HeFH, especially when there is incomplete information to establish a diagnosis and the genetic result affects clinical management	3	C
4. Genetic testing for FH should be carried out using an accredited method in a certified laboratory, using targeted next-generation sequencing of all exons and exon–intron boundaries of *LDLR*, *APOB*, *PCSK9* and *LDLRAP1*, and the exons in *APOB* that encode the LDLR ligand-binding region, as well as analysis for deletions and duplications in *LDLR*	1	A
5. Variants detected by genetic testing should be classified and reported according to contemporary standardized guidelines, for example, those of the ACMG, AMP or ClinGen FH Variant Curation Expert Panel	1	A
6. If a pathogenic or likely pathogenic variant is not detected, FH should not be excluded, particularly if the clinical phenotype is strongly suggestive of FH, because the condition may result from undetected genetic variants	1	A
7. Genetic counselling should be offered, before and after genetic testing, to all individuals suspected of having FH	1	B
8. Genetic counselling should at a minimum include obtaining a three-generation family medical history, risk and psychological assessment, family-based care, enabling of cascade testing, anticipatory guidance and psychological assessment	1	A
9. Pre-conception counselling should be offered to all couples, especially if both partners/parents are known, or suspected, to have FH	1	B
10. Prenatal or pre-implantation genetic testing should be offered if both partners/parents are known to have FH, counselling being particularly important in parents with HeFH who have previously had a child with HoFH	1	C
11. Polygenic scores for hypercholesterolaemia may be useful but are not yet fully standardized, so that they should be used with caution when assessing the differential diagnosis of FH in clinical practice	3	B
12. Cascade genetic testing is highly cost-effective and should be used after a disease-causing variant has been identified in the proband or index case	1	A
13. Pre-test and post-test genetic counselling should be offered to all at-risk relatives as an integral component of cascade testing	1	A
14. Cascade testing should be undertaken using both phenotypic and genotypic approaches (Fig. 1); if genetic testing is not available, a phenotypic approach (that is, a plasma or serum lipid profile, including the LDL-cholesterol concentration) should be used	1	A
15. Cascade genetic testing for the specific variant (variants) identified in the proband (that is, known familial variant testing) should initially be offered to all first-degree relatives; if first-degree relatives are unavailable, or do not wish to undergo testing, known familial variant testing should be offered to at-risk second-degree and then third-degree relatives, with sequential extension to the entire family until all at-risk individuals have been offered testing (Fig. 1)	1	A
16. At-risk children should be offered cascade genetic testing at the earliest opportunity (and more than once if not pursued at the first offer) if an FH-causing variant has been identified in a parent or other first-degree relative	1	A
17. When genetic testing is not feasible, the diagnosis of FH in at-risk relatives should be made phenotypically using age-specific, sex-specific and country-specific LDL-cholesterol concentrations (Fig. 1; Supplementary Material 4); clinical tools for diagnosing FH probands (such as the Dutch Lipid Clinic Network criteria and Simon Broome criteria) are not valid for this purpose. Phenotypic cascade testing should initially be offered to all first-degree relatives. If first-degree relatives are unavailable, or decline testing, phenotypic testing should next be offered to second-degree and then third-degree relatives, with sequential extension to the entire family until all at-risk individuals have been offered testing	1	A
18. 'Reverse' cascade testing (from child to parents) should be offered to parents after a child is identified as a proband with FH, such as after making a diagnosis following a clinical presentation or via a universal or newborn screening programme	1	B

See Fig. 1 for an algorithm for cascade testing of family members. ACMG, American College of Medical Genetics and Genomics; AMP, Association for Molecular Pathology; ClinGen, Clinical Genome Resource; FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia; LDLR, LDL receptor; PCSK9, proprotein convertase subtilisin/kexin type 9.

Clinical recommendations on genetic testing

- all individuals in whom there is a strong suspicion of FH based on clinical and/or family history
- Genetic testing for FH should be carried out using of all exons and exon–intron boundaries of LDLR, APOB, PCSK9 and LDLRAP
- If a pathogenic variant is not detected, FH should not be excluded

Table 4 | Clinical recommendations on risk stratification in patients with familial hypercholesterolaemia

Clinical recommendations	Class	Level
1. Routine assessment and stratification of the risk of ASCVD in all patients with FH should be used to develop effective personalized treatment plans and guide overall management, aiming to maximize reduction in the risk of cardiovascular events and improve quality of life	1	B
2. All patients with FH, including children and adolescents, should be assessed for the presence of heart-healthy behaviours and non-cholesterol risk factors (that is, age, sex, smoking, hypertension, diabetes, obesity and mental health conditions) to stratify the risk of ASCVD	1	B
3. The use of coronary artery disease polygenic risk scores may be considered for stratifying the risk of ASCVD in patients with HeFH, but their value in patient care remains to be established	3	B
4. Additional factors particularly relevant to FH that should be assessed to stratify risk include plasma or serum concentrations of LDL-cholesterol and lipoprotein(a) at diagnosis, LDL-cholesterol life-years, family history of premature ASCVD (especially in first-degree relatives), tendon xanthomas (detected clinically or with imaging) and a positive genetic test result if available	1	A
5. Female-specific factors (such as reproductive history, duration off statin therapy owing to pregnancy and breast feeding, and age at menopause) should be considered when assessing the risk of ASCVD in women with FH	2	B
6. Use of FH-specific cardiovascular risk calculators (such as the SAFEHEART risk equation and the FH Risk Score) should be considered to assess the risk of ASCVD in adult patients with an established diagnosis of HeFH	2	B
7. Cardiovascular risk calculators developed for the general population (such as the Framingham Risk Score, Pooled Cohort Equation, SCORE-2 or QRISK-3) should not be used in patients with FH	1	B
8. In asymptomatic adult patients with HeFH, CACS, CT coronary angiography and carotid ultrasonography may be considered to document the presence and extent of atherosclerotic plaque burden and to guide risk assessment, the timing of initial evaluation being dependent on clinical context and indications	3	B
9. Use of FH-specific cardiovascular risk calculators combined with CACS should be considered to risk stratify adult patients with FH treated with statins	2	B
10. In children and adolescents with HeFH, measurement of carotid intima–media thickness with ultrasonography should not be routinely considered for assessing the risk of ASCVD in clinical practice, because extensive technical expertise is required and clinical value is not established	2	B
11. In children and adolescents with HeFH, CACS, CT coronary angiography and current FH risk calculators (such as the SAFEHEART risk equation or FH Risk Score) should not be used to assess ASCVD risk	1	C
12. In all patients with HoFH, CT coronary angiography (or cardiac catheterization), carotid ultrasonography (or more advanced methods), echocardiography and exercise stress testing should be offered, at initial diagnosis and as clinically indicated (for example, because of cardiac symptoms or a high plaque burden at diagnosis), to assess coronary atherosclerosis (particularly high-risk coronary ostial disease), carotid plaques, atheromatous involvement of the aortic valve (or root), aortic stenosis and inducible myocardial ischaemia, respectively, with the aim of guiding overall management, including the intensity of the cholesterol-lowering therapy	1	B

ASCVD, atherosclerotic cardiovascular disease; CACS, coronary artery calcium scoring; FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia.

risk stratification in patients with FH

- stratification of the risk of ASCVD in all patients with FH
- Use of FH-specific cardiovascular risk calculators (such as the SAFEHEART risk equation and the FH Risk Score) should be considered to assess the risk of ASCVD in adult patients with HeFH
- , Cardiovascular risk calculators developed for the general population (such as the Framingham Risk Score, Pooled Cohort Equation, SCORE-2 or QRISK-3) should not be used in patients with FH

risk stratification in patients with FH

- In children and adolescents with HeFH, CACS, CT coronary angiography and current FH risk calculators (such as the SAFEHEART risk equation or FH Risk Score) should not be used to assess ASCVD risk

- In all patients with HoFH, CT coronary angiography (or cardiac catheterization), carotid ultrasonography (or more advanced methods), echocardiography and exercise stress testing should be offered, at initial diagnosis

Table 6 | Clinical recommendations on the treatment of children with heterozygous familial hypercholesterolaemia

Clinical recommendations	Class	Level
1. At diagnosis, all patients should be offered counselling on following a heart-healthy, low saturated fat (<10% of total calories), high-fibre diet and correcting all other behavioural risk factors for ASCVD, particularly smoking, lack of exercise, obesity and psychological stress	1	B
2. Pharmacological treatment should be offered at age 8–10 years with an LDL-cholesterol concentration >4.9 mmol/l (>190 mg/dl), recorded on two occasions with a fasting lipid profile	1	B
3. Pharmacological treatment should be considered for those aged 8–10 years with an LDL-cholesterol concentration >4.0 mmol/l (>160 mg/dl), recorded on two occasions with a fasting lipid profile, in the presence of multiple ASCVD risk factors or family history of premature ASCVD	2	B
4. Initiation of pharmacological treatment at age <8 years may also be considered with an LDL-cholesterol concentration >4.9 mmol/l (>190 mg/dl), recorded on two occasions	3	B
5. An LDL-cholesterol goal of <3.5 mmol/l (<135 mg/dl) or approximately 50% reduction may be considered in patients with no additional risk factors for ASCVD (for example, diabetes, hypertension, elevated lipoprotein(a) concentration or parental history of ASCVD in the second or third decade of life); non-fasting blood samples may be used to monitor LDL-cholesterol levels in those receiving stable therapy	3	C
6. An LDL-cholesterol goal of <2.5 mmol/l (<100 mg/dl) may be considered in patients with additional risk factors for ASCVD	3	C
7. To achieve LDL-cholesterol treatment goals, the initial medication of choice should be a statin that is approved in the relevant country (or jurisdiction) for use in paediatric patients	1	A
8. Other medications that should be considered, in addition to the maximal tolerated and safe dose of a statin, are ezetimibe and bile acid sequestrants	2	B
9. Use of a PCSK9 inhibitor may be considered according to clinical indications and regulatory approvals, with the caveat of limited evidence of long-term safety in children and adolescents	3	B
10. Plasma levels of liver enzymes, creatine kinase, glucose and creatinine should be measured before starting statin therapy; plasma levels of liver and muscle enzymes and glucose should be monitored as in adults	1	B
11. Growth and adherence to lifestyle management and LDL-cholesterol-lowering medication should be monitored annually or as clinically indicated	1	A
12. Adolescent girls should be offered advice on the basis of current recommendations regarding contraception and the use of lipid-lowering medications in pregnancy	1	B

See Fig. 2 for a simplified treatment algorithm for heterozygous familial hypercholesterolaemia. ASCVD, atherosclerotic cardiovascular disease; PCSK9, proprotein convertase subtilisin/kexin type 9.

treatment of adults with heFH

- . All patients should be offered advice on cardiovascular risk factors (including smoking, hypertension, obesity, metabolic syndrome and diabetes mellitus
- lifestyle modifications
- After approximately 50% reduction in LDL-c
- LDL-c<100 mg/dl in the absence of ASCVD or other major ASCVD risk f
- LDL-c<70 mg/dl) with imaging evidence of ASCVD alone or other major ASCVD risk f
- LDL-cholesterol concentration <55 mg/dl with clinical ASCVD

treatment of adults with heHF

- In patients with a recurrent ASCVD event within 2 years whit statin treatment, a lower LDL-cholesterol goal of <40 mg/dl
- . Maximally tolerated high-potency statins (such as atorvastatin, rosuvastatin or pitavastatin)+_ ezetimibe and/or bempedoic acid
- If LDL goals are not achieved, or bile acid sequestrants such as colesevelam
- PCSK9-I (monoclonal antibodies or a small interfering RNA (inclisiran

treatment of adults with heHF

- In patients with extremely high-risk HeFH (the combination of a high-potency statin, ezetimibe and PCSK9-targeted therapy should be considered as first-line treatment
- Monitoring of therapy with carotid ultrasonography and CT coronary angiography
- LFT, Cr, glu CK measured before starting drug therapy
- LFT monitoring if an increased risk of hepatoxicity)
- CK if musculoskeletal symptoms;
- glu or HbA1c if there are risk factors for diabetes

treatment of children with heHF

- Diet & risk factor modification
- treatment should be offered at age 8–10 years with an LDL-c>190 mg/dl
- aged 8–10 years with an LDL-c>160 mg/dl in the presence of multiple ASCVD risk factors or f. hx of premature ASCVD
- Goal of <135 mg/dl or ~ 50% reduction with no additional risk
- . An LDL-c goal of<100 mg/dl with additional risk factors for ASCVD

treatment of children with heHF

- , the initial medication of choice should be a statin =1 A
- second line: ezetimibe and bile acid sequestrants =2 B
- a PCSK9 inhibitor=3 B
- LFT, CK, glu and cr should be monitored as in adults
- Growth and adherence to lifestyle management medication should be monitored annually

Table 7 | Clinical recommendations on the treatment of patients with homozygous familial hypercholesterolaemia

Clinical recommendations	Class	Level
1. Treatment of patients with HoFH should begin at diagnosis and ideally by the age of 2 years, with counselling on heart-healthy lifestyles, psychological support for the family and LDL-cholesterol-lowering medications	1	B
2. The following treatment goals should be considered: (a) LDL-cholesterol concentration <2.5 mmol/l (<100 mg/dl) in the absence of ASCVD or other major risk factors for ASCVD; (b) LDL-cholesterol concentration <1.8 mmol/l (<70 mg/dl) with imaging evidence of ASCVD alone or additional major risk factors for ASCVD; (c) LDL-cholesterol concentration <1.4 mmol/l (<55 mg/dl) with a previous ASCVD event; fasting and non-fasting blood measurements of LDL-cholesterol concentrations could be used as recommended for patients with HeFH	2	B
3. To achieve LDL-cholesterol goals, all currently approved medications (such as high-potency statin, ezetimibe and colesevelam) should be used; medications should be used sequentially, starting with a statin with rapid up-titration to maximally tolerated and approved doses, followed within 8 weeks by the addition of ezetimibe and possibly colesevelam if tolerated	1	B
4. A PCSK9 inhibitor should be added within a further 8 weeks in patients without biallelic *LDLR* null mutations and continued only after demonstration of an acceptable response (≥15% additional reduction in LDL-cholesterol concentration)	1	B
5. In the highest-risk patients (for example, those with symptomatic ASCVD or multivessel coronary atherosclerosis), the combination of a high-potency statin, ezetimibe and PCSK9-targeted therapy should be strongly considered as first-line treatment	2	B
6. Lipoprotein apheresis should be offered, if feasible, at the age of 3 years (and no later than 8 years) when LDL-cholesterol goals are not achieved with a maximally tolerated regimen of cholesterol-lowering medications	1	A
7. In patients with markedly elevated LDL-cholesterol concentrations when receiving conventional therapy or with rapidly progressive ASCVD, the use of lomitapide (a microsomal triglyceride transfer protein inhibitor) or evinacumab (an angiopoietin-related protein 3 inhibitor) should be considered, adjunctive to diet and conventional drugs, to lower the LDL-cholesterol concentration further, especially if lipoprotein apheresis is not available or feasible	2	B
8. In patients with rapidly progressive ASCVD, the use of evinacumab may be considered, adjunctive to diet, conventional cholesterol-lowering drugs and lomitapide, to lower the LDL-cholesterol concentration further, especially if lipoprotein apheresis is not available or feasible	3	C
9. CT coronary angiography, carotid ultrasonography, echocardiography (including measurement of aortic valve gradients) and exercise stress testing should be used, as clinically indicated, to assess the severity and progression of ASCVD, aortic valve (or root) atheromatous involvement and inducible myocardial ischaemia, as well as to guide overall management and the intensity of LDL-cholesterol lowering treatment	1	B
10. Recommendations made above (Tables 5 and 6) for the management of HeFH should be followed concerning control of behavioural and non-cholesterol cardiovascular risk factors, blood sampling to monitor cholesterol-lowering therapy, use of aspirin, treatment of FH during acute illness, use of vaccinations (including for SARS-CoV-2), treatment of cardiovascular sequelae of COVID-19, blood testing protocol for monitoring drug safety and potential toxicities, assessment of growth in children and pre-pregnancy counselling of adolescent girls	1	*
11. Liver transplantation should be considered in patients with HoFH and rapidly progressive ASCVD who do not attain guideline-recommended LDL-cholesterol goals when receiving all available treatment, including lipoprotein apheresis (or who cannot tolerate lipoprotein apheresis or do not have access to suitable lipoprotein apheresis services), and are considered psychologically suitable for this treatment; combined liver and heart transplantation from a single donor should also be considered in the most severely affected patients	2	B
12. Liver transplantation may be considered in patients with HoFH and minimal or stable ASCVD who do not attain an LDL-cholesterol goal of <10 mmol/l (<400 mg/dl) when receiving all available LDL-cholesterol-lowering treatments; this situation will typically apply to children and young adults with severe biallelic null variants in *LDLR*	3	C

See Fig. 3 for a simplified treatment algorithm for homozygous familial hypercholesterolaemia (FH). ASCVD, atherosclerotic cardiovascular disease; COVID-19, coronavirus disease 2019; HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia; LDLR, LDL receptor; PCSK9, proprotein convertase subtilisin/kexin type 9; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. *See Tables 5 and 6 for levels of evidence for patients with HeFH pertaining to each of the items listed in recommendation 10.

treatment of patients with hoHF

- Treatment of HoFH should begin at diagnosis and ideally by the age of 2 years, with counselling on heart-healthy lifestyles
- treatment goals
- LDL-c<100 mg/dl) in the absence of ASCVD
- LDL-c<70 mg/dl) with imaging evidence of ASCVD alone
- LDL-c<55 mg/dlwith a previous ASCVD event

treatment of patients with hoHF

- statin with rapid up-titration to maximally tolerated, followed within 8 weeks by the addition of ezetimibe and possibly colesevelam if tolerated
- A PCSK9 i added within a 8 weeks in without biallelic LDLR null mutations and continued only after response (≥15% additional reduction in LDL-c)
- In the highest-risk the combination of a high-potency statin, ezetimibe and PCSK9-targeted therapy strongly considered as first-line treatment

the treatment of patients with hoFH

- Lipoprotein apheresis should be offered, if feasible, at the age of 3 years (and no later than 8 years) when LDL-cholesterol goals are not achieved
- In markedly elevated or with rapidly progressive ASCVD, the use of lomitapide (a microsomal triglyceride transfer protein inhibitor) or evinacumab (an angiopoietin-related protein 3 inhibitor)
- , use of aspirin, use of vaccinations, blood testing protocol for monitoring drug safety and potential toxicities, assessment of growth in children and pre-pregnancy counselling of adolescent girls

the treatment of patients with hoHF

- Liver transplantation should be considered in patients with HoFH
- rapidly progressive ASCVD who do not attain LDL-c goals when receiving all available treatment, including lipoprotein apheresis
- Liver transplantation in HoFH and minimal or stable ASCVD who do not attain an LDL-c goal 400 mg/dl children and young with severe biallelic null variants in LDLR

Table 8 | Clinical recommendations on the treatment of familial hypercholesterolaemia during pregnancy

Clinical recommendations	Class	Level
1. All women with FH who are of child-bearing age, including adolescents, should be educated about the risks of pregnancy; advice on safer and preferred methods of contraception, with minimal cardiovascular risk, and the importance of contraception should be reinforced to prevent unplanned pregnancy	1	B
2. Reinforcement and optimization of heart-healthy behaviours, including diet, physical activity and psychological well-being, should be prioritized before, during and after pregnancy and breastfeeding	1	B
3. Pre-pregnancy counselling should be offered to all women before starting a statin, ezetimibe, PCSK9 inhibitor or other lipid-modifying therapies, and this advice should be reinforced as clinically indicated	1	B
4. Assessment of ASCVD using imaging (for example, CT angiography for coronary artery disease or echocardiography for aortic stenosis) should be offered to women with HoFH or high-risk HeFH before a planned pregnancy	1	B
5. Given that LDL-cholesterol and triglyceride concentrations increase during pregnancy, assessment of plasma lipids and lipoprotein levels should not routinely be considered, unless the results will be used to change management, as in women with HoFH	2	B
6. Bile acid sequestrants should be considered to treat hypercholesterolaemia, ideally 3 months before a planned pregnancy, as well as during pregnancy and lactation; routine monitoring for malabsorption of fat-soluble vitamins (particularly vitamin K with an international normalized ratio) and folate should also be considered	2	B
7. Statins and other systemically absorbed cholesterol-lowering drugs should ideally be discontinued 3 months before planned conception and during pregnancy and lactation. If a woman with FH becomes pregnant while taking a statin, ezetimibe, a PCSK9 inhibitor or other lipid-modifying therapies, this treatment should be stopped, and she should be reassured that this therapy is unlikely to harm the fetus	1	B
8. In women with HoFH and clinical ASCVD, the continued use of statin therapy should be considered; use of statins, ezetimibe, PCSK9 monoclonal antibodies or other lipid-modifying therapies should particularly be considered after the first trimester, especially if the LDL-cholesterol goal is not achieved and lipoprotein apheresis is not available or feasible	2	B
9. Lipoprotein apheresis should be continued or initiated during pregnancy in women with HoFH, especially in those with established ASCVD and in whom LDL-cholesterol levels are not at guideline-recommended goal; similar advice applies to women with severe HeFH, including those with a lipoprotein(a) concentration ≥125 nmol/l (≥60 mg/dl)	1	B

ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia; PCSK9, proprotein convertase subtilisin/kexin type 9.

treatment of FH during pregnancy

- Pre-pregnancy
  - educated about the risks of pregnancy
  - heart-healthy behaviours, including diet, physical activity
  - . Assessment of ASCVD using imaging in women with HoFH or high-risk HeFH
  - assessment of lipids levels should not routinely be considered unless for changing management, as in women with Hohf

treatment of FH during pregnancy

- Bile acid sequestrants 3 months before pregnancy, as well as during pregnancy and lactation;
  - routine monitoring vitamin K and folate should also be considered

Statins and other systemically absorbed cholesterol-lowering drugs should ideally be discontinued 3 months before planned conception during pregnancy and lactation.

treatment of FH during pregnancy

- In women with HoFH and clinical ASCVD, the continued use of statin therapy should be considered; use of statins, ezetimibe, PCSK9 therapies should particularly be considered after the first trimester

- Lipoprotein apheresis should be continued or initiated during pregnancy in HoFH, established ASCVD;

Table 9 | Clinical recommendations on the treatment of familial hypercholesterolaemia by lipoprotein apheresis

Clinical recommendations	Class	Level
1. Lipoprotein apheresis should be undertaken, if feasible, in children (aged ≥3 years and <8 years) and adults with HoFH who do not achieve guideline-recommended LDL-cholesterol goals, despite maximally tolerated, combination drug therapy	1	A
2. Lipoprotein apheresis should be undertaken in adults with phenotypic HeFH and progressive ASCVD who do not achieve LDL-cholesterol goals despite combined treatment with a high-potency statin, ezetimibe and a PCSK9 inhibitor, especially those with a lipoprotein(a) concentration ≥125 nmol/l (≥60 mg/dl)	1	B
3. Vascular access for lipoprotein apheresis should initially be via peripheral veins, but an arteriovenous fistula may be needed if peripheral venous access becomes impossible, which may be particularly relevant to children. Central venous catheters are not recommended except in an emergency or as a temporary measure	1	B
4. Onefold to twofold plasma volumes (body weight in kg×0.045 l) or blood volumes [plasma volume/(1 − haematocrit)] should be treated weekly or fortnightly in a specialized setting (a lipid clinic, nephrology unit or blood transfusion centre). Plasma exchange requires a smaller extracorporeal blood volume than lipoprotein apheresis and is recommended as an alternative in children with a body weight <30 kg	1	A
5. All diet and drug therapy to lower LDL-cholesterol concentrations should be continued during treatment with lipoprotein apheresis, and comprehensive psychosocial support should be offered to all patients receiving lipoprotein apheresis	1	A
6. Routine full blood counts should be monitored regularly, and iron supplementation initiated if iron-deficiency anaemia develops in patients with FH receiving long-term lipoprotein apheresis	1	A
7. Angiotensin-converting enzyme inhibitors should not be used in patients undergoing lipoprotein apheresis based on apolipoprotein B adsorption, and angiotensin-receptor blocking agents should be substituted	1	A
8. Patients receiving anticoagulants, such as warfarin, will require dose adjustment or discontinuation several days before an apheresis procedure that uses intravenous heparin, but antiplatelet therapy should be maintained. Direct oral anticoagulants (such as apixaban, dabigatran or rivaroxaban) need only be stopped on the day of apheresis because of their shorter half-life	1	B
9. The cholesterol-lowering efficacy of lipoprotein apheresis should be monitored by measuring acute reductions in LDL-cholesterol and lipoprotein(a) concentrations (ideally 65–70%) and by calculating the interval mean (C_{mean}) between consecutive procedures, using the Kroon formula: $C_{mean}=C_{min}+k(C_{max}-C_{min})$, for which C_{max} is the pre-procedure value and C_{min} is the post-procedure value. Values for k are 0.65 for LDL-cholesterol in patients with HoFH and 0.71 for LDL-cholesterol in patients with HeFH receiving statin therapy and undergoing lipoprotein apheresis at fortnightly intervals. Comparison of interval means with the recommended LDL-cholesterol goals for patients with HoFH should be used to adjust the volume of blood or plasma to be treated and/or the frequency of lipoprotein apheresis procedures as necessary	1	B
10. Because the rate of rebound of plasma lipoprotein(a) levels after lipoprotein apheresis is similar to that of plasma LDL-cholesterol levels in patients with HeFH, a value for k of 0.71 in the Kroon formula should be considered appropriate when estimating the interval (intercycle) mean concentration of lipoprotein(a); this value may be used to adjust the lipoprotein apheresis regimen to achieve a therapeutic goal of <90 nmol/l (<43 mg/dl) in patients with elevated lipoprotein(a) concentrations	2	B
11. In children and adults with HoFH and aortic root or coronary artery disease, the effect of lipoprotein apheresis on disease progression should be monitored at least annually by echocardiography or coronary angiography, respectively. The latter procedure is also applicable to patients with HeFH with coronary disease and should be performed as and when indicated	1	B
12. Adjunctive therapy with a PCSK9 inhibitor, either evolocumab or alirocumab, should be attempted in all patients with FH before starting or while receiving lipoprotein apheresis. These therapies will be effective mainly in patients with HeFH and often may replace lipoprotein apheresis. Injected therapeutic agents should be administered soon after, but not immediately before, a lipoprotein apheresis procedure	1	B
13. Adjunctive therapy with lomitapide or evinacumab should be considered in patients with HoFH, particularly in those with progressive ASCVD, who do not reach guideline-recommended LDL-cholesterol goals while receiving lipoprotein apheresis combined with statin, ezetimibe and a PCSK9 inhibitor. This adjunctive therapy increases LDL-cholesterol lowering and may reduce the frequency of lipoprotein apheresis and, if tolerated, sometimes replaces it	2	B
14. When lomitapide or evinacumab is first selected in preference to lipoprotein apheresis, adjunctive use of lipoprotein apheresis should be considered in all patients with HoFH who do not reach guideline-recommended LDL-cholesterol goals	2	B

ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia; PCSK9, proprotein convertase subtilisin/kexin type 9.

treatment of FH by lipoprotein apheresis

- Lipoprotein apheresis
  - children (aged ≥3 years and <8 years) and adults with HoFH who do not achieve LDL-c goals, despite maximally tolerated, combination drug therapy

adults HeFH and progressive ASCVD who do not achieve LDL-c goals despite especially those with a lipoprotein(a) ≥60 mg/dl

Onefold to twofold plasma volumes (body weight in kg × 0.045 l) or blood volumes [plasma volume/(1 − haematocrit)] should be treated weekly or fortnightly

Plasma exchange requires a smaller extracorporeal blood volume in children with a body weight <30 kg

the treatment of FH by lipoprotein apheresis

- Continue diet and drug therapy
- blood counts should be monitored
- supplementation initiated if iron-deficiency anaemia
- oral anticoagulants need be stopped
- monitored at least annually by echo or coronary angiography

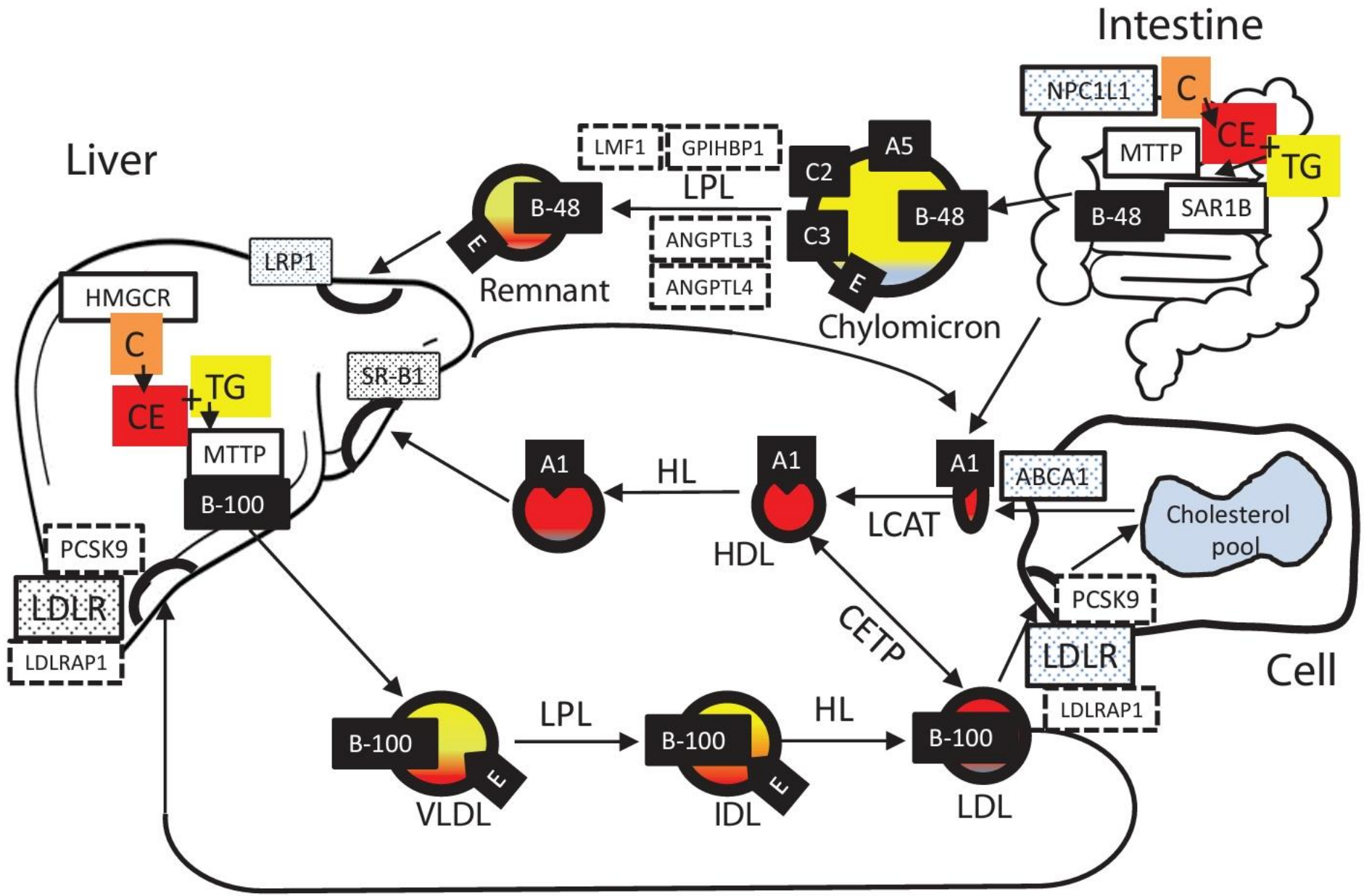
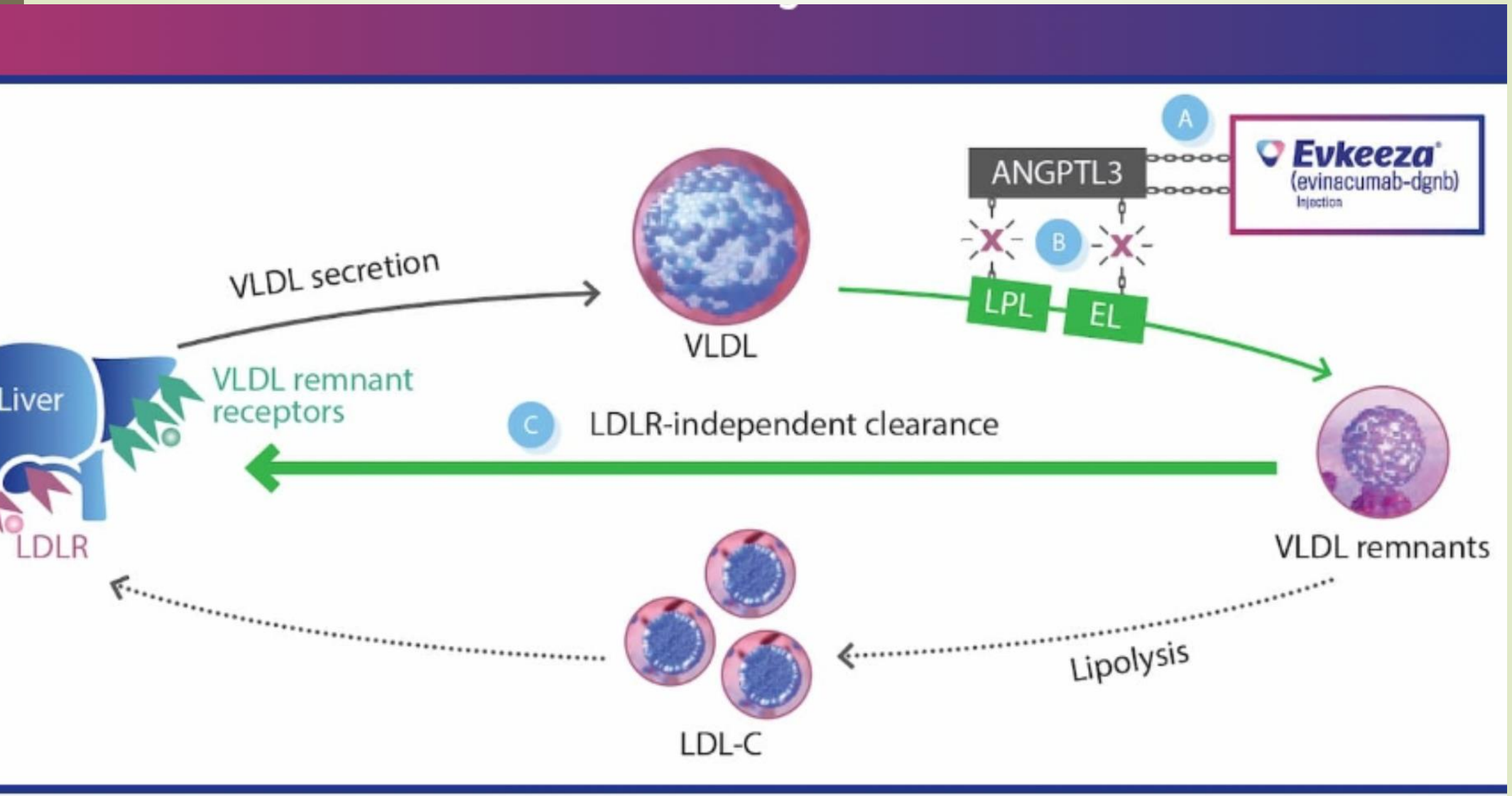


Figure 1. Schematic of plasma lipoprotein metabolism. See text for detailed explanation and abbreviations. Yellow, TG; red, cholesterol ester; orange, free cholesterol; black boxes, apolipoproteins; stippled boxes, receptors or transporters; dashed box borders, accessory proteins.


A
ANGPTL3
Evkeeza
(evinacumab-dgnb)
Injection
B
LPL
EL
VLDL secretion
VLDL
Liver
VLDL remnant
receptors
C
LDLR-independent clearance
LDLR
VLDL remnants
Lipolysis
LDL-C