Rare dyslipidaemias, from phenotype to genotype to management: a European Atherosclerosis Society task force consensus statement

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Genome sequencing and gene-based therapies appear poised to advance the management of rare lipoprotein disorders and associated dyslipidaemias. However, in practice, underdiagnosis and undertreatment of these disorders are common, in large part due to interindividual variability in the genetic causes and phenotypic presentation of these conditions. To address these challenges, the European Atherosclerosis Society formed a task force to provide practical clinical guidance focusing on patients with extreme concentrations (either low or high) of plasma low-density lipoprotein cholesterol, triglycerides, or high-density lipoprotein cholesterol. The task force also recognises the scarcity of quality information regarding the prevalence and outcomes of these conditions. Collaborative registries are needed to improve health policy for the care of patients with rare dyslipidaemias.

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Introduction

What is a rare disease? Although a universal definition is elusive, the average global prevalence threshold for a rare disease is estimated to be 40–50 cases per 100 000 people, varying according to descriptors used by individual countries.[1] Criteria used by regulatory agencies in Europe and the USA are broadly in line with this estimate (table 1).[2,3]

Although each rare disease affects a small number of people, collectively these conditions pose a considerable health burden. Indeed, with over 7000 rare diseases identified to date, as many as one in 12 people, or approximately 36 million people in Europe (and perhaps 500 million people worldwide cumulatively), are affected.[4] Management of rare disorders therefore represents a major challenge for clinicians, payers, and policy makers to reduce the disease-associated burden. Patients and their families often endure a protracted diagnostic process before the correct diagnosis is made.[5] Because more than 80% of rare diseases have a genetic cause, genomic analysis plays a crucial role in both diagnosis and management, and in driving development of novel treatments.

Progress in the field of rare dyslipidaemias, together with the decreasing cost of genome sequencing and bioinformatics, seems to argue for a precision medicine approach for the management of patients with rare dyslipidaemias. Yet the reality for clinical practice often trails behind. Several factors could explain this lag, including the scarcity of high-quality information about the prevalence of these disorders, interindividual variability in phenotypic expression, and uncertainty regarding the relative importance of phenotype versus genotype in the care pathway. Moreover, the recognition that small-effect genetic variants might collectively influence phenotypic expression under a polygenic framework provides further diagnostic challenges.[6] All of these factors create impediments to the diagnosis, management, and access to treatments for rare dyslipidaemias.

This consensus statement from the European Atherosclerosis Society (EAS) task force aims to address these uncertainties by providing a theoretical background to the underlying pathophysiology, and practical clinical guidance, for rare lipoprotein disorders associated with extreme concentrations (either low or high) of LDL cholesterol, triglycerides, and HDL cholesterol. Although genetic testing has a clear role in definitive diagnosis, it is predominantly the phenotypic expression that determines the course of clinical management.

Overview of rare lipoprotein disorders

At least 25 monogenic dyslipidaemias are defined by extreme biochemical deviations with or without physical features, and typically follow patterns of autosomal dominant, codominant, or recessive inheritance.[7] These

	Definition	Cases per 100 000 people
European Medicines Agency[2]	A life-threatening or chronically debilitating condition that affects ≤5 per 10000 people in the EU	50
US Food and Drug Administration[3]	Any disease or condition that, first, affects <200000 people in the USA or, second, affects >200000 people in the USA and for which there is no reasonable expectation that the cost of developing a drug and making it available in the USA for a disease or condition will be recovered from sales in the USA of such a drug	64

Table 1: **Agency definitions of a rare disease: Europe versus USA**

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	Inheritance	Gene	Chromosome	MIM reference number(s)
↑ LDL-cholesterol (hyperbetalipoproteinaemia)				
Familial hypercholesterolaemia	ACD	*LDLR*	19p13	143890, 606945
Familial defective apolipoprotein B-100	ACD	*APOB*	2p24	144010, 615558, 107730
Autosomal dominant hypercholesterolaemia subtype 3	ACD	*PCSK9*	1p32	603776, 607786
Autosomal recessive hypercholesterolaemia	AR	*LDLRAP1*	1p35	603813, 605747
Sitosterolaemia (phytosterolaemia)	AR	*ABCG5*	2p21	210250, 605459
Sitosterolaemia (phytosterolaemia)	AR	*ABCG8*	2p21	210250, 605460
Atypical dominant hypercholesterolaemia	AD	*APOE*	19q13	107741
Lysosomal acid lipase deficiency	AR	*LIPA*	10q23	278000, 613497
↓ LDL-cholesterol (hypobetalipoproteinaemia)				
Abetalipoproteinaemia	AR	*MTTP*	4q23	200100, 157147
Homozygous hypobetalipoproteinaemia	ACD	*APOB*	2p24	144010, 615558, 107730
Chylomicron retention disease (Anderson disease)	AR	*SAR1B*	5q31	246700, 607690
Familial combined hypolipidaemia	ACD	*ANGPTL3*	1p31	605019, 604774
PCSK9 deficiency	ACD	*PCSK9*	1p32	605019, 607786
↑ Triglycerides				
Monogenic chylomicronemia (formerly type 1 HLP)				
LPL deficiency	AR	*LPL*	8p22	609708, 238600
Apolipoprotein C-II deficiency	AR	*APOC2*	19q13	207750, 608083
Apolipoprotein A-V deficiency	AR	*APOA5*	11q23	145750, 144650, 606368
Lipase maturation factor 1 deficiency	AR	*LMF1*	16p13	246650, 611761
GPIHBP1 deficiency	AR	*GPIHBP1*	8q24	612757, 615947
Infantile hypertriglyceridaemia, transient	AR	*GPD1*	12q13	614480, 138420
Dysbetalipoproteinaemia (formerly type 3 hyperlipoproteinaemia)	Complex	*APOE*	19q13	107741, 617347
↓HDL-cholesterol (hypoalphalipoproteinaemia)				
Tangier disease	ACD	*ABCA1*	9q31	205400, 600046
Apolipoprotein A-I deficiency	ACD	*APOA1*	11q23	604091, 107680
LCAT deficiency; fish eye disease	ACD	*LCAT*	16q22	245900, 136120, 606967
↑ HDL-cholesterol (hyperalphalipoproteinaemia)				
Cholesteryl ester transfer protein deficiency	ACD	*CETP*	16q13	143470, 118470
Scavenger receptor B1 deficiency	ACD	*SCARB1*	12q24	610762, 601040
Hepatic lipase deficiency	AR	*LIPC*	15q21	614025, 151670

ABCA1=gene encoding ATP-binding cassette protein type A1. *ABCG5*=gene encoding ATP-binding cassette protein type G5. *ABCG8*=gene encoding ATP-binding cassette protein type G8. ACD=autosomal codominant (meaning that heterozygotes express an abnormal biochemical phenotype about half as extreme as homozygotes). AD=autosomal dominant. *ANGPTL3*=gene encoding angiopoietin-related protein 3. *APOA1*=gene encoding apolipoprotein A1. *APOA5*=gene encoding apolipoprotein A-V. *APOB*=gene encoding apolipoprotein B. *APOC2*=gene encoding apolipoprotein C-II. *APOE*=gene encoding apolipoprotein E. AR=autosomal recessive. *CETP*=gene encoding cholesteryl ester transfer protein. *GPD1*=gene encoding glycerol-3-phosphate dehydrogenase 1. *GPIHBP1*=gene encoding glycosylphosphatidylinositol-anchored HDL-binding protein 1. HLP=hyperlipoproteinaemia. LCAT=lecithin cholesterol acyl transferase. *LCAT*=gene encoding LCAT. *LDLR*=gene encoding the low-density lipoprotein receptor. *LDLRAP1*=gene encoding low-density lipoprotein receptor adapter adaptor protein 1. *LIPA*=gene encoding lysosomal acid lipase. *LIPC*=gene encoding hepatic lipase. LPL=gene encoding lipoprotein lipase. *LPL*=gene encoding LPL. *LMF1*=gene encoding lipase maturation factor 1. MIM=Mendelian Inheritance in Man. *MTTP*=gene encoding microsomal triglyceride transfer protein. *PCSK9*=gene encoding the enzyme proprotein convertase subtilisin/kexin type 9. *SAR1B*=gene encoding GTP-binding protein SAR1b. *SCAR1B*=gene encoding scavenger receptor 1B.

Table 2: **Monogenic lipoprotein disorders by phenotype**

conditions are caused by rare mutations affecting a total of 23 known genes (table 2). This causal framework informs the design of diagnostic targeted DNA-sequencing (so-called pan dyslipidaemia) panels[7] and defines bioinformatic parameters to show variant profiles from whole genome or exome sequencing results. Mutations in different genes might occasionally produce an identical phenotype (eg, in dominant forms of familial hypercholesterolaemia), and in other cases contrasting mutations (ie, loss-of-function *vs* gain-of-function) within the same gene could cause opposite phenotypes (eg, mutations in *APOB* and *PCSK9* causing either high or low concentrations of LDL cholesterol). A schematic overview of lipoprotein metabolism focusing on gene products that cause monogenic dyslipidaemias is provided in figure 1.

LDL-related disorders

Apolipoprotein B-containing lipoproteins comprise LDL, intermediate-density lipoproteins (including those that correspond to the remnants of very-low density lipoprotein [VLDL] particles), VLDL, chylomicrons and their remnant particles, and lipoprotein(a). All are

pro-atherogenic and play key roles in the transport of cholesterol and triglycerides in the circulation.[8] These particles represent the historical beta and pre-beta lipoprotein electrophoretic mobility class.

Disorders characterised by very high concentrations of LDL cholesterol

Pathophysiology

Hyperbetalipoproteinaemia is characteristic of several rare dyslipidaemias with markedly increased LDL cholesterol concentrations or apolipoprotein B-100 concentrations as the defining feature. These conditions predominantly result from impairment of the interaction between the LDL particle and the LDL receptor. The resulting clinical disorder is familial hypercholesterolaemia, in which the core defect is delayed clearance of LDL from the plasma, resulting in hypercholesterolaemia, physical signs (including arcus cornealis, xanthelasmas, and tendon xanthomas; figure 2) and, if untreated, premature atherosclerotic cardiovascular disease.[9]

There are numerous comprehensive reviews on the diagnosis and management of familial hypercholesterolaemia.[9,10] Heterozygous familial hypercholesterolaemia is the most common inherited metabolic disorder causing atherosclerotic cardiovascular disease, affecting one individual per 200–250 individuals.[9,10] Because heterozygous familial hypercholesterolaemia is not a rare disorder (by both European and US definitions of the term), we do not cover it in depth in this consensus statement. By contrast, homozygous familial hypercholesterolaemia is a very rare disease that affects approximately one individual per 160 000–300 000 people globally.[11]

Familial hypercholesterolaemia is an autosomal co-dominant disorder. Most individuals with genetically confirmed heterozygous familial hypercholesterolaemia and those with homozygous familial hypercholesterolaemia have one and two mutant alleles of the *LDLR* gene, respectively, conferring either defective or null LDL receptor functionality. Heterozygous mutations in other genes, including *APOB* and *PCSK9*, explain less than 10% of cases of heterozygous familial hypercholesterolaemia, and two mutant alleles of these genes and of *LDLRAP1* (also called *ARH*, for autosomal recessive hypercholesterolaemia), produce a phenotype that resembles homozygous familial hypercholesterolaemia.[11,12]

More than 2300 unique familial hypercholesterolaemia-causing mutations have been identified in the *LDLR* gene.[13] Of the *APOB* mutations, Arg3527Gln (arginine to glutamine at residue 3527), is the most frequently observed and disrupts the interaction of apolipoprotein B with the LDL receptor[14] About 50 additional likely pathogenic *APOB* mutations are associated with hyperlipidaemia,[13] many involving arginine residues within the receptor-binding domain that is encoded mainly by exon 26.[14] More than 30 gain-of-function mutations in the gene encoding proprotein convertase subtilisin/kexin type 9 (PCSK9) have been reported in patients with familial hypercholesterolaemia; together these mutations account for less than 1% of all cases of familial hypercholesterolaemia.[15] Until more consistent data emerge, ultrarare *STAP1* gene mutations are not considered to cause familial hypercholesterolaemia. Finally, at least 20% of patients referred to a lipid

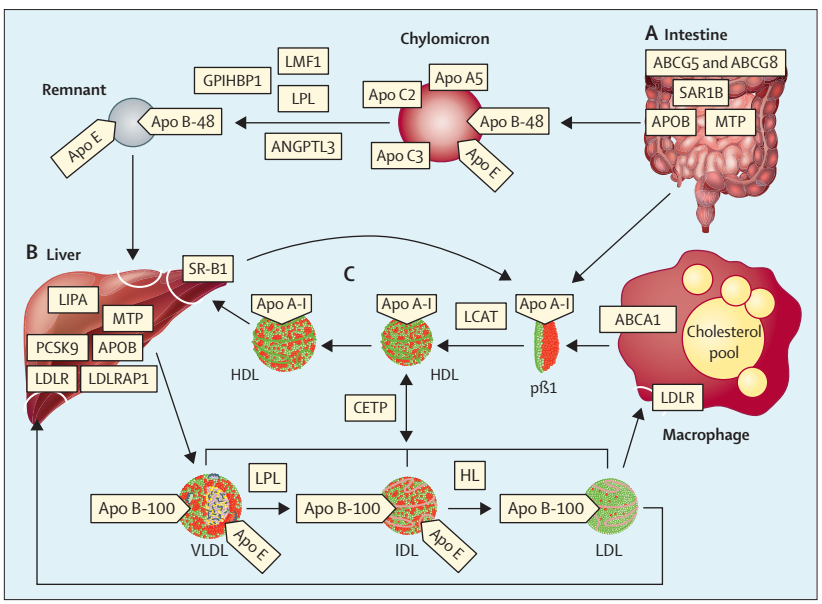

Figure 1: **Lipid metabolism focusing on causal factors in rare dyslipidaemias**
Apolipoprotein B-containing lipoproteins are produced by the intestine (A) and liver (B). Tissue-specific editing of APOB RNA produces either shorter apolipoprotein B-48 (in the intestine) or full-length apolipoprotein B-100 (in the liver) to serve as the scaffold of particle assembly. Exogenous dietary fatty acids and sterols are actively absorbed; plant sterols are immediately re-secreted into the intestinal lumen by ABCG5 and ABCG8 half-transporters. Exogenous and endogenous (ie, newly synthesised) lipids within enterocytes and hepatocytes, respectively, are packaged into lipoprotein precursors by MTP, which catalyses co-translational transfer of triglyceride to nascent apolipoprotein B-48 or B-100 during assembly of chylomicrons in enterocytes or VLDL particles in hepatocytes. Chylomicron formation also requires SAR1B. After traversing the intestinal lymphatics, chylomicrons enter the circulation, where the triglyceride content is hydrolysed by LPL, resulting in the delivery of fatty acids to local tissues. LMF1 is an intracellular chaperone required for secretion of LPL, whereas GPIHBP1 stabilises LPL at the endothelial surface. Apolipoprotein C-II and apolipoprotein A-V promote LPL activity, whereas apolipoprotein C-III and ANGPTL3 inhibit LPL activity. The remodeled smaller lipoprotein remnants are cleared by receptor-mediated mechanisms involving apolipoprotein E. Circulating triglyceride-rich VLDL similarly undergoes LPL-mediated hydrolysis (with similar relationships to interacting molecules, not shown) forming smaller IDL, which is further processed by HL to yield cholesterol-rich LDL that, in turn, delivers cholesterol to peripheral cells. Some LDLs are ultimately catabolised by the hepatic LDLR. Because apolipoprotein B-100 uniquely contains the receptor-binding domain, it is the responsible ligand for the LDLR.[6] The LDL–LDLR complex is internalised and transits though a well characterised pathway that requires LDLRAP1. LDL contents are degraded in lysosomes by LIPA, releasing cholesterol, suppressing intracellular cholesterol synthesis, and stimulating esterification. LDLRs can recycle to the cell surface multiple times, a process that is terminated by PCSK9. LDL lipids within lysosomes are degraded by LIPA. Reverse cholesterol transport is shown in (C). Apolipoprotein A-I produced by the liver and intestine constitutes the primary protein of HDL particles. ABCA1 is ubiquitously expressed and effluxes phosphatidylcholines and unesterified cholesterol from the plasma membrane to lipid-poor apolipoprotein A-I or pβ1-HDL and small HDL particles. pβ1-HDL is transformed to a small, discoidal particle that is the target of LCAT, which is activated by apolipoprotein A-I, uses phosphatidylcholine and unesterified cholesterol as substrates, and generates cholesteryl esters. LCAT-derived cholesteryl esters are transferred by CETP to VLDL and LDL, or directly delivered to the liver via SR-BI. ABCA1=ATP-binding cassette transporter A1. ABCG5=ATP-binding cassette protein 5. ABCG8=ATP-binding cassette protein 8. ANGPTL3=angiopoietin like protein 3. Apo=apolipoprotein. CETP=cholesteryl ester transfer protein. GPIHBP1=glycosylphosphatidyl-inositol-anchored high density lipoprotein-binding protein 1. HL=hepatic lipase. IDL=intermediate density lipoprotein. LCAT=lecithin-cholesterol acyltransferase. LDLR=hepatic LDL receptor. LDLRAP1=LDL receptor-associated protein. LIPA=lysosomal acid lipase. LMF1=lipase maturation factor 1. LPL=lipoprotein lipase. MTP=microsomal triglyceride-transfer protein. pβ1= prebeta1-HDL. PCSK9=proprotein convertase subtilisin/kexin type 9. SAR1B=SAR1 homolog B GTPase. SR-BI=scavenger receptor.

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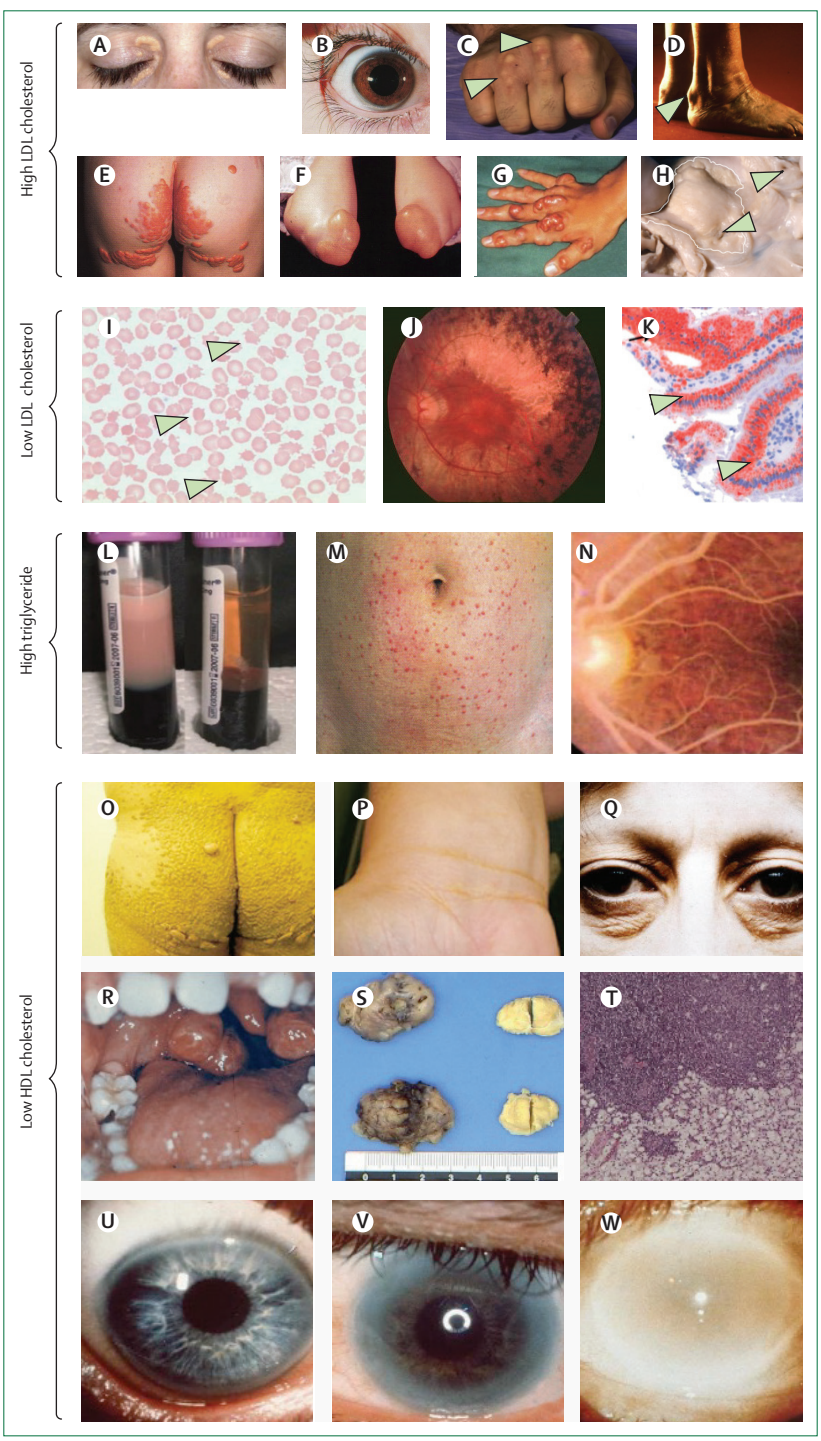
clinic with suspected heterozygous familial hypercholesterolaemia carry polygenic susceptibility to high concentrations of LDL cholesterol.[16] A detailed discussion of polygenic aetiologies of dyslipidaemias is beyond the scope of this consensus statement; the interested reader can access other reviews on this topic.[6,17]



Clinical presentation and diagnosis

Given the remit of this consensus statement, we focus on patients with extremely increased LDL cholesterol concentrations, essentially homozygous familial hypercholesterolaemia (figure 3), which is very rare. Historically, a treated LDL cholesterol concentration of greater than 8 mmol/L (>300 mg/dL) or untreated LDL cholesterol concentration of greater than 10 mmol/L (>400 mg/dL), together with the presence of cutaneous or tendon xanthomas evident before the age of 10 years, was considered sufficient for the diagnosis of homozygous familial hypercholesterolaemia, although it is now recognised that clinical presentation might vary, in large part because of the genetic heterogeneity of familial hypercholesterolaemia.[11] Diagnosis still primarily depends on clinical assessment; scoring systems can be helpful, as is targeted DNA sequencing when biallelic pathogenic mutations are shown in known causative genes. Patients with homozygous familial hyper-cholesterolaemia most often have pathogenic mutations in the *LDLR* gene, usually two different mutations (compound heterozygotes) or, more rarely, the same mutation (simple or true homozygotes).[11,17] The severity of the plasma LDL cholesterol elevation and clinical features depend both on the underlying causative gene and the type of mutation, although there is considerable interindividual variability.[11,17] Because the individual LDL cholesterol concentration, rather than mutation type, is the key determinant of the

Figure 2: **Clinical findings in selected rare dyslipidaemias**
(A–H) High LDL-cholesterol disorders: familial hypercholesterolaemia. (A) Xanthelasmas; (B) arcus cornealis in a 5-year-old girl with homozygous familial hypercholesterolaemia; (C) extensor tendon xanthomas (arrows); (D) Achilles tendon xanthomatosis (arrow); (E) raised planar xanthomas in homozygous familial hypercholesterolaemia; (F) elbow tubero-eruptive xanthomas in homozygous familial hypercholesterolaemia; (G) severe tuberous xanthomatosis of the hands in a patient with autosomal recessive hypercholesterolaemia; (H) post-mortem dissected aortic valve region from a 5-year-old girl with sitosterolaemia showing severe atherosclerosis within the white line and occluded coronary artery ostia (indicated by arrows). (I–K) Low LDL-cholesterol syndromes. (I) Acanthocytes (arrows) on peripheral blood smear (abetalipoproteinaemia or homozygous hypobetalipoproteinaemia); (J) atypical retinitis pigmentosa on fundoscopy (abetalipoproteinaemia or homozygous hypobetalipoproteinaemia); (K) fat-filled enterocytes (arrows) on microscopy with triglyceride staining red (as seen in abetalipoproteinaemia, homozygous hypobetalipoproteinaemia or chylomicron retention disease). (L–N) High triglyceride disorders: monogenic chylomicronaemia. (L) Lipaemic plasma on left (normal plasma on right); (M) eruptive xanthomas on abdomen; (N) lipaemia retinalis on fundoscopy. (O–W) Low HDL-cholesterol disorders. (O–Q) Planar xanthomas in patients with apolipoprotein A-I deficiency; (R–T) enlarged tonsils of patients with Tangier disease; (U–W) age-dependent progression of corneal opacities in patients with lecithin-cholesterol acyltransferase deficiency. Similar opacities are seen in patients with apolipoprotein A-I deficiency who are homozygous or hemizygous for structural apolipoprotein A-I variants. Pictures B, E–H, and M are reproduced from Davignon and Dufour,[101] by permission of Clinical Publishing. Pictures C and D are reproduced from Genest and colleagues, by permission of Elsevier.[102] Picture J is reproduced from Hamel.[103] Picture K is reproduced from Sassolas and colleagues.[104] Pictures L and N are reproduced from Yuan and colleagues, by permission of *CMAJ*.[105] Pictures O and P were reproduced from Santos and colleagues,[79] by permission of Elsevier. Pictures S and T were reproduced from Ravesloot and colleagues,[106] by permission of Elsevier. All other images were from the authors' own personal collections.

atherosclerotic cardiovascular disease risk, treatment intensity should be tailored accordingly.[11]

Other rare dyslipidaemias can have a clinical presentation similar to homozygous familial hypercholesterolaemia, albeit usually with lower LDL cholesterol concentrations (figure 3). β-sitosterolaemia (phytosterolaemia), an autosomal recessive disorder due to mutations in *ABCG5* and *ABCG8*, encoding the ATP-binding cassette (ABC) sub-family G members 5 and 8, respectively, results in retention of non-cholesterol sterols, and is characterised by atypical xanthomatosis with increased concentrations of plant sterols and stanols (phytosterols) with and without increased LDL cholesterol concentrations, and with variable susceptibility to early atherosclerotic cardiovascular disease (figure 2). Very occasionally, some milder cases of increased LDL cholesterol, together with hepatosplenomegaly and variable triglyceride concentrations, result from lysosomal acid lipase deficiency (also called cholesterol ester storage disease or, in paediatric patients, Wolman disease), which is an autosomal recessive disorder of the *LIPA* gene.[18] Definitive diagnosis for these other rare conditions is by DNA sequencing.

Current and future therapy

Management of homozygous familial hypercholesterolaemia builds on algorithms for heterozygous familial hypercholesterolaemia that are well established and typically involve the combination of maximally tolerated statin, ezetimibe, and a PCSK9 inhibitor, in addition to diet and lifestyle.[9–11] Moreover, for homozygous familial hypercholesterolaemia, lipoprotein apheresis is considered to be foundational, given the severity of LDL cholesterol increases, profound atherosclerosis risk, and refractoriness to other treatments.[11,19] Treatment in homozygous familial hypercholesterolaemia can be guided by genetic testing because the PCSK9 monoclonal antibody evolocumab is ineffective in individuals with two null *LDLR* mutations but can show efficacy when defective *LDLR* mutations are present. PCSK9 antibodies are effective when biallelic gain-of-function PCSK9 mutations are present (figure 3).[20] The oral microsomal triglyceride transfer protein inhibitor lomitapide is another adjunctive therapeutic option in patients with homozygous familial hypercholesterolaemia.[21,22] The effectiveness of this treatment is maximised with adherence to a low-fat diet (<20% of energy derived from fat) with dosing outside of mealtimes to minimise gastrointestinal symptoms; however, hepatic steatosis can result as a consequence of the drug's mechanism of action. Mipomersen, a second-generation apolipoprotein B antisense oligonucleotide, had been available in the USA until May, 2018, when sales were discontinued due to safety concerns, including increased liver transaminases and fatty liver disease. Mipomersen is not licensed in Europe. Evinacumab (a monoclonal antibody to ANGPTL3) and *LDLR* gene therapy could offer therapeutic potential as adjunctive therapies.[22,23] Rarely, liver transplantation in patients with homozygous familial hypercholesterolaemia could be considered.[11] If sitosterolaemia is diagnosed, the treatment is markedly different: apheresis is not required, and the hyperlipidaemia often responds well if dietary sterol intake is reduced, and to treatment with ezetimibe or bile acid sequestrants.[24] If lysosomal acid lipase deficiency is diagnosed, treatment includes enzyme replacement by infusion of sebelipase alfa.[25]

Management of people with homozygous familial hypercholesterolaemia merits consideration of a wide range of other issues relating to genetic counselling, cascade screening to identify family members affected with heterozygous familial hypercholesterolaemia and, in female patients, contraception and pregnancy. For further information, readers are referred to additional reviews.[9–11]

Disorders characterised by very low LDL cholesterol concentrations

Primary hypobetalipoproteinaemia refers to a group of inherited dyslipidaemias characterised by very low or

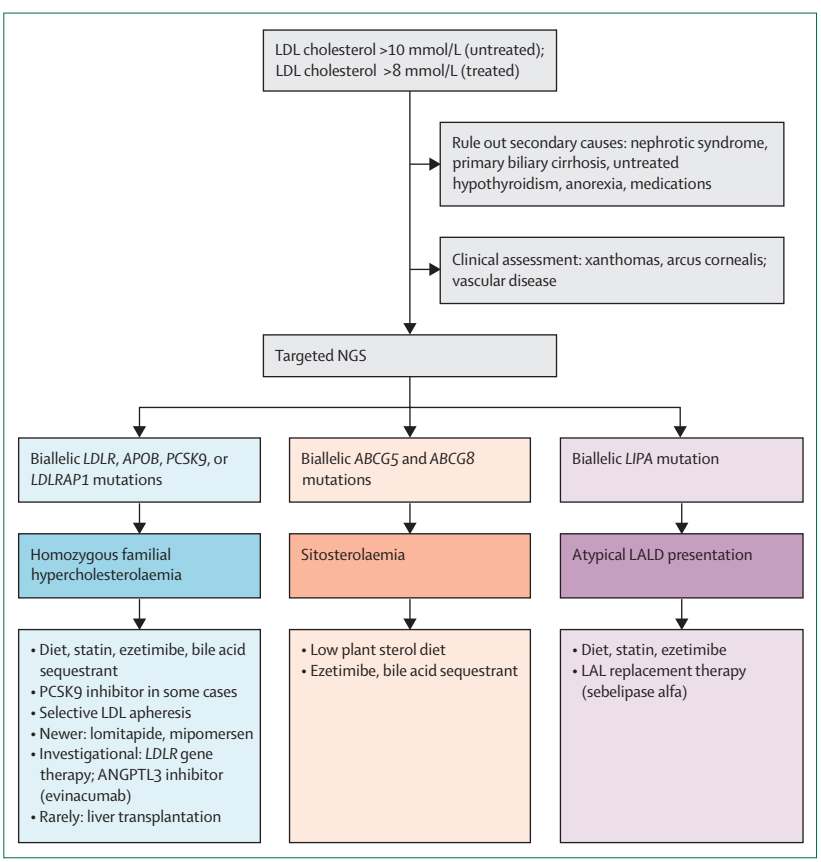


Figure 3: **Algorithm for the diagnosis and management of lipoprotein disorders characterised by very high concentrations of LDL cholesterol**

ABCG5 and *ABCG8*=genes encoding the ATP-binding cassette sub-family G members 5 and 8. ANGPTL3=angiopoietin-related protein 3. *APOB*=gene encoding apolipoprotein B. LAL=lysosomal acid lipase. LALD=lysosomal acid lipase deficiency. *LDLR*=gene encoding the low-density lipoprotein receptor. *LDLRAP1*=gene encoding low-density lipoprotein receptor adaptor protein 1. *LIPA*=gene encoding lysosomal acid lipase. NGS=next generation sequencing. *PCSK9*=gene encoding the enzyme proprotein convertase subtilisin/kexin type 9.

absent plasma LDL cholesterol and apolipoprotein B concentrations. Other lipids and lipoproteins can also be involved, depending on the specific gene and severity of the mutation or mutations (table 2).[26,27]

Pathophysiology

Hypobetalipoproteinaemia can result from decreased production or increased catabolism of apolipoprotein B containing lipoproteins. Loss-of-function mutations in the *MTTP* gene, encoding microsomal triglyceride transfer protein (MTP), cause abetalipoproteinaemia (also called Bassen–Kornzweig syndrome), an autosomal recessive disorder characterised by the absence of VLDL and chylomicron production, conferring undetectable plasma concentrations of LDL cholesterol and apoli-poprotein B, and very low concentrations of triglycerides and total cholesterol (<0·33 mmol/L or <30 mg/dL).[28] To date, over 30 different loss-of-function mutations in the *MTTP* gene have been described, all of which ultimately impair the ability to lipidate nascent apolipoprotein B-containing lipoproteins.[28]

Homozygous familial hypobetalipoproteinaemia (FHBL) clinically resembles abetalipoproteinaemia. FHBL is an autosomal co-dominant disorder involving the *APOB* gene and is characterised by very low concentrations of apolipoprotein B (lower than the fifth percentile for age and sex) and LDL cholesterol (usually <1·0 mmol/L or <38·7 mg/dL).[29] FHBL-causing mutations in *APOB* compromise the integrity of the lipoprotein particle, in contrast to the mutations affecting binding to the LDL receptor, which cause the opposite phenotype (ie, familial hypercholesterolaemia). Over 60 different pathogenic mutations in *APOB* outside the receptor-binding domain have been associated with structural protein defects, often with secretion of truncated forms of apolipoprotein B (ie, apolipoprotein B-9 [which corresponds to 9% of the full protein length] to apolipoprotein-B-89 [which corresponds to 89% of the full protein length]), decreased secretion of VLDL, and increased catabolism of VLDL and LDL, resulting in reductions in circulating concentrations of cholesterol and triglycerides.[30–32] Other causes of primary hypobetalipoproteinaemia include loss-of-function mutations in *SAR1B*, the gene encoding Sar1 homolog B GTPase, *ANGPTL3*, the gene encoding angiopoietin-related protein 3, and *PCSK9*. Biallelic mutations in *SAR1B* cause autosomal recessive chylomicron retention disease (also known as Anderson disease), which is characterised by failure of chylomicron secretion from enterocytes.[33] By contrast, loss-of-function mutations in *ANGPTL3* cause familial combined hypolipidaemia, although the mechanism is incompletely understood (table 2).[34,35] In addition, over 30 different loss-of-function mutations in *PCSK9* result in reduced lysosomal degradation of the LDL receptor, with increased recycling to the cell surface, which drives increased catabolism of LDL particles, thereby reducing LDL cholesterol concentrations.[15]

Clinical presentation and diagnosis

Figure 4 provides an algorithm for the diagnosis and management of disorders characterised by very low LDL cholesterol concentrations. Abetalipoproteinaemia and homozygous FHBL are associated with undetectable concentrations of LDL cholesterol and of apolipoprotein B on direct assay; concentrations of triglycerides are very low and almost all plasma cholesterol is carried by HDL particles. Because exogenous fat-soluble vitamins are absorbed via chylomicrons and transported via apolipoprotein B-containing lipoproteins, the defects in abetalipoproteinaemia, homozygous FHBL, and chylomicron retention disease lead to severe fat-soluble vitamin deficiencies. Clinical manifestations (figure 2) include acanthocytosis with mild anaemia from birth, fat malabsorption, and growth failure in early childhood; later onset of features of fat soluble vitamin deficiency include night blindness, atypical retinitis pigmentosa, osteomalacia or rickets, posterior column signs, spinocerebellar ataxia, peripheral neuropathy, and prolonged prothrombin time (or international normalised ratio).[28,29,33] A differentiating feature is that obligate heterozygote parents of patients with homozygous FHBL have reduced LDL cholesterol concentrations, whereas parents of patients with abetalipoproteinaemia have normal lipid profiles. Patients with heterozygous hypobetalipoproteinaemia also have increased risk of hepatic steatosis, but concurrently reduced risk of atherosclerotic cardiovascular disease.[28]

Chylomicron retention disease might be considered if there is a failure to thrive in infancy, together with severe malabsorption with steatorrhoea, and fat soluble vitamin deficiency.[33] Chylomicron retention disease is characterised by relatively normal triglyceride concentrations, with absence of apolipoprotein B-48 and chylomicrons after a fat load, and less severe eye involvement than in abetalipoproteinaemia. Obligate heterozygote parents of children with chylomicron retention disease have normal lipid profiles. By contrast, in heterozygotes for ANGPTL3 deficiency, concentrations of total cholesterol, LDL cholesterol, and triglycerides are approximately 50% lower than normal with relatively normal HDL cholesterol, whereas homozygotes have very suppressed concentrations of total cholesterol, LDL cholesterol, triglycerides, and HDL cholesterol, albeit without associated vitamin deficiencies or other specific clinical manifestations, and probable protection from atherosclerotic cardiovascular disease.[34,35] Individuals with biallelic *PCSK9* loss-of-function mutations have LDL cholesterol concentrations that are less severely suppressed than in abetalipoproteinaemia, homozygous FHBL, or chylomicron retention disease; these individuals have no deleterious clinical phenotype.[36] Diagnosis is confirmed when pathogenic mutations are detected by DNA sequencing.[15] During the tests of patients with hypobetalipoproteinaemia, secondary causes (eg, chronic liver disease, chronic pancreatitis, cystic fibrosis, end-stage renal disease, hyperthyroidism,

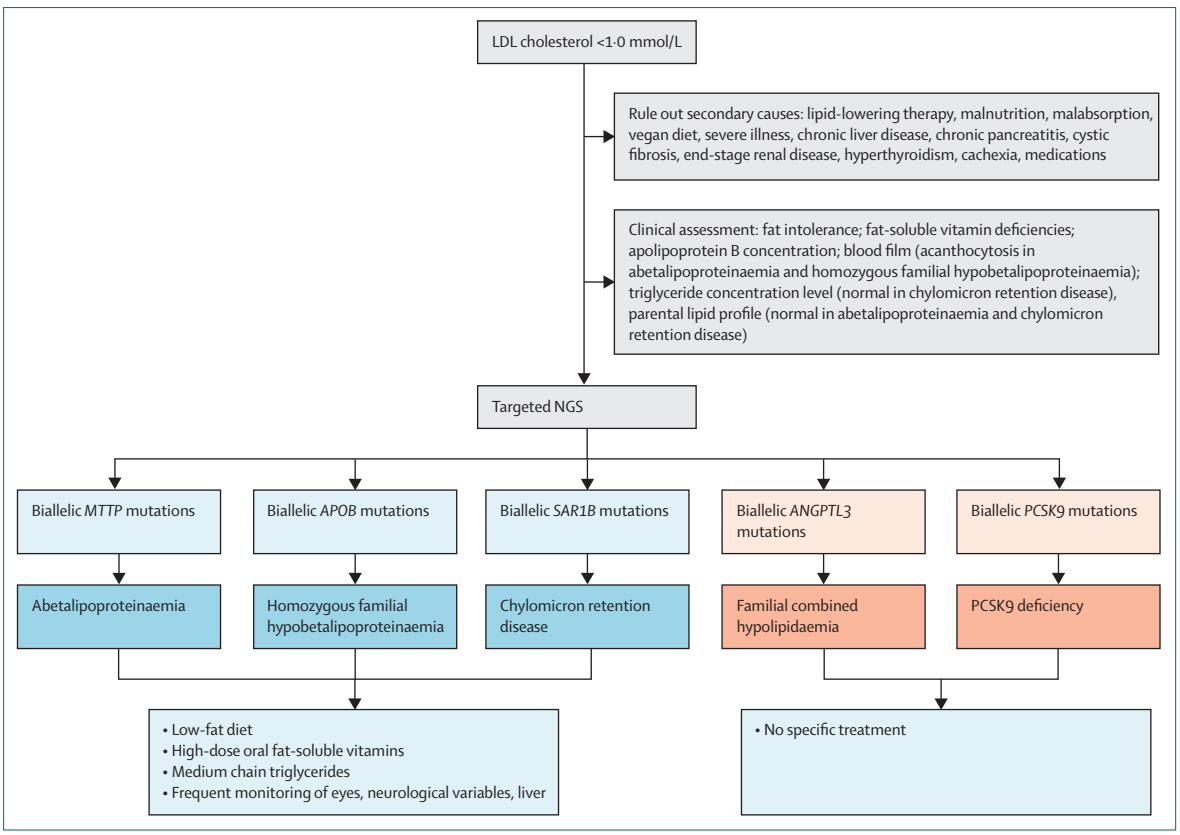


Figure 4: **Algorithm for the diagnosis and management of lipoprotein disorders characterised by very low or undetectable concentrations of LDL cholesterol**
ANGPTL3=gene encoding angiopoietin-related protein 3. *APOB*=gene encoding apolipoprotein B. *MTTP*=gene encoding microsomal triglyceride transfer protein. NGS=next generation sequencing. *PCSK9*=gene encoding the enzyme proprotein convertase subtilisin and kexin type 9. *SAR1B*=gene encoding GTP-binding protein SAR1b.

cachexia, and malabsorption) should be excluded (figure 4).[26,27]

Current therapy

Early diagnosis and treatment are essential to prevent long term ophthalmological and neurological complications for patients with abetalipoproteinaemia, homozygous FHBL, and chylomicron retention disease. The overall principles of management for these three conditions include fat-restricted diet (with or without medium chain triglycerides), supplementation of essential fatty acids, and high oral doses of vitamins A, D, E, and K, which can largely correct the deficiencies, presumably through the medium chain triglyceride pathway via the portal vein.[26–29] No specific management is required for carriers of biallelic loss-of-function mutations in *PCSK9* and *ANGPTL3*. Heterozygous first-degree relatives have either normal lipid profiles (for *MTTP* and *SAR1B* gene mutations) or mild to moderate hypolipidaemia (for *APOB*, *PCSK9*, and *ANGPTL3* gene mutations). Patients carrying a heterozygous loss-of-function mutation in *APOB* can exhibit fatty liver.[26–29,37] Although the clinical sequelae and therapeutic management of this complication have not been established, supplementation with fat-soluble vitamins to correct possible deficiencies could be recommended. Conversely, hypobetalipoproteinaemia associated with *ANGPTL3* or *PCSK9* loss-of-function mutations appears to represent a benign or even a protective condition, whereby specific treatment is not required.

Chylomicronaemia syndromes

Hypertriglyceridaemia has been defined as fasting triglyceride concentrations of greater than 2·0 mmol/L or greater than 180 mg/dL (although some consider the threshold to be >1·7 mmol/L or >150 mg/dL). Severe hypertriglyceridaemia, defined as a triglyceride concentration of greater than 10 mmol/L (>885 mg/dL), affects 0·1–0·2% of the population. Fasting triglycerides concentrations that are increased to this degree almost always indicate the pathological presence of chylomicrons.[38] Within this group, most individuals with identified genetic causes have a polygenic predisposition, defined as an accumulation of common variants with small individual effects on triglycerides concentrations or heterozygous, rare, incompletely penetrant loss-of-function mutation (or mutations).[39] At most, 1–2% of adults with severe hypertriglyceridaemia

have a monogenic cause, defined as recessive (biallelic), rare, large-effect variants (ie, either simple homozygosity or compound heterozygosity), in genes involved in regulating triglyceride-rich lipoprotein metabolism.[39] The widely used term familial chylomicronaemia syndrome is synonymous with our preferred term of monogenic chylomicronaemia. Notably, compared with patients who have much more prevalent multifactorial or polygenic chylomicronaemia, individuals with monogenic chylomicronaemia have the following characteristics: tend to express their hypertriglyceridaemia phenotype at a younger age, including childhood; are less likely to be obese or have secondary factors; can have fasting triglycerides concentrations in excess of 20 mmol/L (1780 mg/dL); have a higher lifetime risk of developing acute pancreatitis (ie, up to 60–70% *vs* 5–10% in multifactorial chylomicronaemia); have much lower apolipoprotein B-100 concentrations; and are very resistant to triglyceride-lowering medications.

Pathophysiology

Although hepatic overproduction of VLDL is the most common cause of mild to moderate hypertriglyceridaemia, monogenic severe hypertriglyceridaemia instead results from severely or completely impaired lipoprotein lipase (LPL)-mediated lipolysis of triglyceride-rich lipoproteins, particularly large chylomicrons carrying high amounts of triglycerides. Chylomicrons are secreted by the intestine after consumption of a fat-containing meal and cleared from the circulation after 4–6 h so they cannot be detected in the fasting state. Specifically, rare biallelic loss-of-function mutations in *LPL*, or in four other genes encoding proteins that activate or interact with LPL are considered causative for familial chylomicronaemia syndrome.[38] Causes of monogenic chylomicronaemia are summarised in table 2.

Monogenic chylomicronaemia syndrome

To date, biallelic loss-of-function mutations in five genes involved in the catabolism of chylomicron triglycerides cause monogenic chylomicronaemia—ie, *LPL* (encoding lipoprotein lipase; LPL), *APOC2* (encoding apolipoprotein C-II), *APOA5* (encoding apolipoprotein A-V), *LMF1* (encoding lipase maturation factor 1 [LMF1]), and *GPIHBP1* (encoding glycosylphosphatidylinositol-anchored HDL-binding protein 1 [GPIHBP1]).[38–41] All these gene products are required for LPL-mediated lipolysis of chylomicrons and VLDL. However, concentrations of VLDL can be normal or low because VLDL secretion is driven largely by triglycerides brought to the liver by chylomicron remnants. VLDL secretion can be increased if the metabolic syndrome (ie, central obesity, insulin resistance, and diabetes) is also present. More than 80% of individuals with monogenic chylomicronaemia have biallelic *LPL* mutations, of which more than 100 have been identified.[38,41]

Apolipoprotein C-II is the required co-activator of LPL. Although biallelic loss-of-function mutations in *APOC2* cause a phenotype that is essentially identical to homozygous LPL deficiency, molecular testing indicates that only 2–5% of individuals with monogenic chylomicronaemia have biallelic *APOC2* mutations.[41] Similarly rare is the complete absence of apolipoprotein A-V, which is thought to facilitate the interaction of chylomicrons and VLDL with LPL at the surface of the capillary endothelium. Biallelic loss-of-function mutations in *APOA5* are seen in 2–5% of individuals with monogenic chylomicronaemia,[41] who can present with a phenotype similar to LPL deficiency, although the severity often depends on secondary factors, such as insulin resistance or diabetes.

LMF1, identified as the cause of murine combined lipase deficiency, is a protein required for proper folding and intracellular trafficking of nascent LPL.[42] LMF1 deficiency leads to markedly reduced LPL secretion, causing severe hypertriglyceridaemia similar to LPL deficiency.[42] Patients with biallelic mutations in *LMF1* represent 1–2% of all monogenic severe hypertriglyceridaemia.[41]

Finally, GPIHBP1 translocates newly secreted LPL across capillary endothelium and stabilises the enzyme on the endothelial surface, where it interacts with chylomicrons and VLDL.[43] Biallelic mutations in *GPIHBP1*, including large-scale gene deletions[41,44] underlying complete GPIHBP1 deficiency, are the second most common cause of monogenic chylomicronaemia, representing 5–10% of cases.[41]

Characterisation of monogenic chylomicronaemia indicates similar severity across a wide range of lipid and metabolic phenotypes associated with biallelic *LPL* mutations versus patients with mutations in the four minor genes.[41] Being overweight or insulin resistant further exacerbates the phenotype.[38,41]

Other proposed monogenic causes of severe hypertriglyceridaemia

Complete loss of GPD1 (glycerol-3-phosphate dehydrogenase 1) activity has been reported in transient childhood hypertriglyceridaemia, and probably results from increased hepatic secretion of VLDL triglycerides rather than chylomicrons.[45] Other genes with large effect mutations contributing to severe hypertriglyceridaemia include *CREB3L3*, encoding transcription factor cyclic AMP-responsive element-binding protein H,[46] and *GCKR*, encoding glucokinase regulatory protein.[47] Rare heterozygous loss-of-function variants in these genes contribute to polygenic susceptibility, as described in the following section (polygenic or multifactorial chylomicronaemia). Finally, severe hypertriglyceridaemia is sometimes a secondary feature of rare monogenic forms of insulin resistance or diabetes, including familial generalised or partial lipodystrophies.

Polygenic or multifactorial chylomicronaemia

Many clinicians believe that patients with severe hypertriglyceridaemia must have a monogenic condition. However, severe hypertriglyceridaemia is most often due

to polygenic susceptibility interacting with secondary non-genetic factors.[6] For example, in a study[39] of 563 patients with triglyceride concentrations of greater than 885 mmol/L, only 6 (1·1%) patients had biallelic mutations in monogenic chylomicronaemia genes, and 87 (15%) patients were heterozygous carriers of a loss-of-function mutation in one of these genes versus only 20 (4·0%) out of 503 patients with normolipidaemia. An even larger number of patients with severe hypertriglyceridaemia have an excessive burden of common DNA polymorphisms, each of which raises triglycerides concentrations by only a fraction of a mmol/L. By chance, some individuals inherit a preponderance of triglyceride-raising polymorphisms, which cumulatively increase the risk of developing severe hypertriglyceridaemia. For example, in the patients with severe hypertriglyceridaemia discussed above, 180 (32%) out of 563 patients had an extreme accumulation of 32 triglyceride-raising common variants versus 48 (9·5%) out of 473 patients in controls.[39] This three-times-higher susceptibility to hypertriglyceridaemia is typical for a polygenic trait; the disease risk in genetically predisposed people is increased, but not absolute, because a fraction of heathy controls also carry the same genotypic burden. Secondary factors are frequently present in genetically predisposed individuals who express hypertriglyceridaemia.

Clinical presentation

Clinical features associated with chylomicronaemia are summarised in panel 1 and figure 2. Severe hypertriglyceridaemia caused by monogenic loss-of-function mutations in one of the five genes involved in lipolysis often presents in childhood, even infancy, commonly involving failure to thrive and gastrointestinal symptoms such as abdominal pain and pancreatitis.[38] A lipaemic blood sample will indicate the presence of hypertriglyceridaemia-induced acute pancreatitis.[38] In older adolescents and adults who have avoided early-onset pancreatitis, diagnosis might be made during routine blood testing for other reasons. Acute pancreatitis can affect any patient with a triglyceride concentration of greater than 10 mmol/L (885 mg/dL). While the relative risk is higher in monogenic chylomicronaemia, in absolute terms hyper-triglyceridaemia-induced pancreatitis is seen much more frequently with multifactorial or polygenic chylo-micronaemia.[48] Whatever the genetic basis, the severity of hypertriglyceridaemia (and thus propensity to develop pancreatitis) is increased by consumption of high-fat foods, alcohol, oestrogen-containing medications, pregnancy, obesity and insulin resistance, diabetes, hypothyroidism, or medications that increase VLDL secretion (eg, steroids).[38] Because both parents will be obligate heterozygotes for any of these genes, screening of siblings of an affected child is obligatory; a quarter of siblings will also have biallelic or homozygous mutations. The lipid phenotype in heterozygous parents or siblings can vary from normal to severe hypertriglyceridaemia.[39]

Panel 1: **Clinical features associated with chylomicronaemia syndrome**

- Abdominal pain
- Recurrent acute pancreatitis
- Hepatosplenomegaly
- Eruptive xanthomatosis
- Lipaemia retinalis
- Fatigue
- Memory loss
- Depression
- Vomiting and diarrhoea
- Proteinuria
- Anaemia

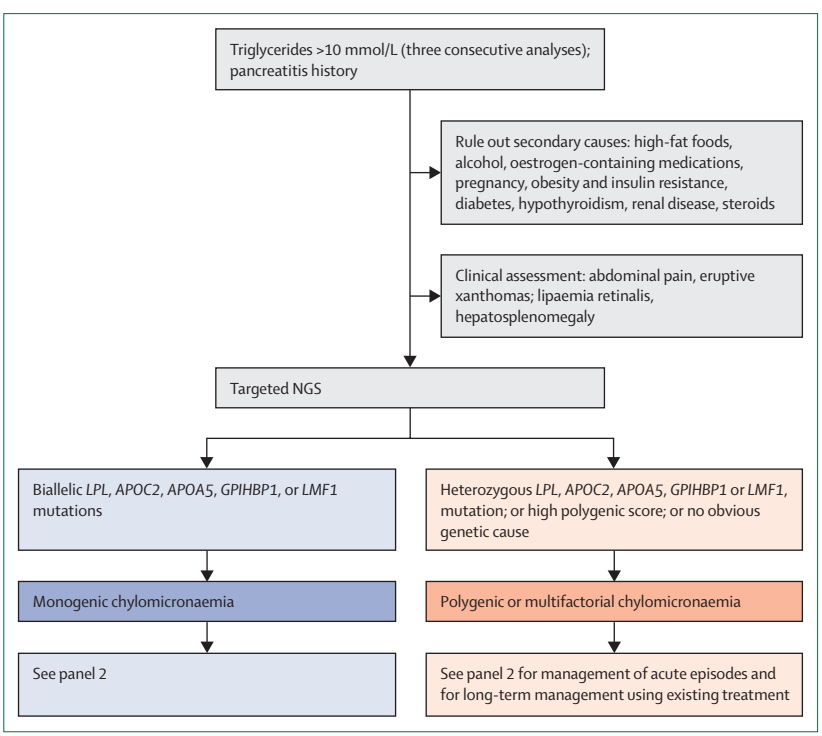


Figure 5: **Algorithm for the diagnosis of severe hypertriglyceridaemia**
APOA5=gene encoding apolipoprotein A-V. *APOC2*=gene encoding apolipoprotein C-II. *GPIHBP1*=gene encoding gl ycosylphosphatidylinositol-anchored HDL-binding protein 1. *LMF1*=gene encoding lipase maturation factor 1. *LPL*=gene encoding lipoprotein lipase. NGS=next generation sequencing.

Diagnosis and treatment

Diagnosis of monogenic chylomicronaemia should be considered in cases in which plasma triglyceride concentrations are greater than 10 mmol/L (>885 mg/dL), especially when triglycerides far exceed this concentration (figure 5). As mentioned, most patients with such triglyceride concentrations have multifactorial or polygenic chylomicronaemia; the proportion with monogenic chylomicronaemia might only be 1–2%.[39] The absence of secondary factors, and diagnosis at a very early age, are suggestive of monogenic chylomicronaemia, particularly if hypertriglyceridaemia is associated with

Panel 2: **Treatment of chylomicronaemia syndrome**

Long-term diet and pharmacological intervention

- Adherence to a low-fat diet; recommended at <10% of calories from fat (although compliance among patients is poor)
- Avoidance of alcohol
- Reduction of intake of high glycaemic food items
- Intake of medium chain fatty acids for caloric supplementation and dietary variety
- Supplementation with high doses (4 g) of omega-3 fatty acids, although this is relatively ineffective for patients with monogenic chylomicronaemia
- Fibrate therapy, although relatively ineffective for patients with monogenic chylomicronaemia

During episodes of acute pancreatitis

- Complete fasting during the first few days, with parenteral fluid support and analgesia
- Intravenous insulin for patients with diabetes
- Plasmapheresis or plasma exchange is generally not recommended

Newer or investigational treatments

- *LPL* gene therapy (alipogene tiparvovec)
- Anti-APOC3 antisense therapies (volanesorsen; AKCEA-APOCIII-LRx)
- Anti-ANGPTL3 therapies (evinacumab; IONIS-ANGPTL3-LRx)

pancreatitis.[48] Low plasma concentrations of plasma apolipoprotein B (<0·75 g/L) might help differentiate patients with monogenic versus multifactorial chylomicronaemia.[48] A history of severe hypertriglyceridaemia in a sibling also suggests a strong genetic basis for this disorder. Clearly, however, differentiating monogenic severe hypertriglyceridaemia from other more complex causes, such as the combination of heterozygous plus polygenic predisposition, is key.[39,48] Genetic testing for the five genes involved in LPL-mediated lipolysis, plus a polygenic score for hypertriglyceridaemia, could be useful to clarify the genetic basis.[7]

Therapy centres around consumption of a low-fat diet, with ideally less than 10% of calories from fat (panel 2). However, adherence to such a regimen is extremely challenging for most patients. The use of medium-chain fatty acids can provide calories and essential fatty acids, while preventing increases in concentrations of plasma triglyceride.[38] Fibrates, which increase LPL activity, are typically not useful in patients with monogenic chylomicronaemia, but can be effective in patients with polygenic chylomicronaemia. High doses (4 g) of omega-3 fatty acids, which have been shown to reduce concentrations of VLDL and possibly chylomicron secretion, can also be effective in individuals with polygenic hypertriglyceridaemia, and the small quantity of added dietary fat is offset by the potential efficacy of this therapy.[38]

During an episode of acute pancreatitis, complete fasting is usually very effective during the first few days of treatment.[49] Hydration and analgesia are also important, as is control over secondary factors; in patients with diabetes, intravenous insulin therapy can also be helpful. Although plasma exchange has sometimes been advocated in this situation, there is no evidence that this procedure positively affects short-term or long-term outcomes more than conservative management.[49] Moreover, without ongoing metabolic control, triglyceride concentrations rapidly rebound. Therefore, with the possible exception of controlling severe hypertriglyceridaemia due to monogenic chylomicronaemia during pregnancy,[50] the use of plasmapheresis is not recommended.[49]

The limitations of available treatments are clear; typically, patients with monogenic chylomicronaemia have triglyceride concentrations of greater than 20 mmol/L, even with good dietary compliance and adherence to available medications. The risk of pancreatitis is always present and more effective therapies are needed. Treatments on the horizon, including biological agents that reduce apolipoprotein C-III or ANGPTL3, offer the possibility of substantially reducing concentrations of plasma triglycerides in individuals without LPL activity from monogenic causes.[22] Concerns regarding thrombocytopenia associated with treatment involving the original anti-APOC3 antisense agent volanesorsen in monogenic chylomicronaemia are partially mitigated by a next-generation anti-APOC3 agent.[51] Nonetheless, volanesorsen was approved for use in Europe in 2019. LPL gene therapy (alipogene tiparvovec) was approved for use in Europe in 2012, but the sponsor did not renew the license after 2017.[22]

Dysbetalipoproteinaemia

Dysbetalipoproteinaemia (formerly known as broad β disease or hyperlipoproteinaemia type 3) affects one to two people per 20 000 people.[52] Both triglycerides and cholesterol are variably increased due to pathological accumulation of intermediate-density lipoprotein or VLDL remnants. Although it biochemically resembles mixed dyslipidaemia, dysbetalipoproteinaemia can be distinguished by measuring apolipoprotein B concentrations.[53] Distinctive clinical findings include palmar and tuberoeruptive xanthomas on the elbows and knees. Patients are prone to developing premature coronary disease and, especially, peripheral arterial disease. Most affected individuals are homozygous for the APOE ε2 isoform, which encodes a protein that has defective binding to the LDL receptor, leading to accumulation of apolipoprotein B-48 chylomicron remnants in the circulation. About 10% of patients have a large-effect dominant rare missense variant in *APOE*. However, because normolipidaemic individuals also have these genotypes, additional susceptibility factors, including insulin resistance or diabetes, are required together with secondary non-genetic factors (eg, exogenous hormones, poor diet, hypothyroidism, renal disease, diabetes,

	Very low HDL cholesterol(<0·5 mmol/L)	Moderately low HDL cholesterol (<0·5–0·9 mmol/L)
Underlying diseases	Severe hypertriglyceridaemia, uncontrolled diabetes, liver failure (acute hepatic failure, congested liver/right heart failure, primary biliary liver cirrhosis), systemic or acute inflammation, haemato-oncological diseases (acute lymphoblastic leukaemia, chronic myelogenous leukaemia, multiple myeloma)	Moderate hypertriglyceridaemia, type 2 diabetes, obesity, chronic inflammation, growth hormone excess, hypercortisolism, chronic kidney disease
Lifestyle	NA	Smoking, physical inactivity
Drugs	Androgens (testosterone, anabolic drugs), probucol	Thiazide diuretics, some β-blockers, antiretroviral drugs

NA=not applicable.

Table 3: **Secondary causes of low HDL cholesterol**

paraproteinaemia, or systemic lupus erythematosus). Treatment includes control of secondary factors and use of either statin or fibrate therapy, or both.

Monogenic hypotriglyceridaemia

No reported single gene disorders lower triglycerides exclusively. This biochemical feature is typically a component of multisystem conditions characterised by low to absent apolipoprotein B-containing lipoproteins as discussed above, such as abetalipoproteinaemia, FHBL, and ANGPTL3 deficiency. APOC3 deficiency is associated with reduced triglycerides and increased HDL cholesterol, with reduced atherosclerotic cardiovascular disease risk.[54] The reduced triglyceride concentrations in these conditions have minimal to no clinical consequences per se; treatment should follow the general recommendations for these disorders.

HDL-related disorders

Plasma concentrations of HDL cholesterol are routinely measured in a lipid panel for two main reasons: first, to estimate LDL cholesterol concentrations in the absence of direct measurement[55] and, second, to estimate cardiovascular disease risk, given evidence from epidemiological studies that low HDL cholesterol concentrations are associated with increased risk for atherosclerotic cardiovascular disease.[56] HDL fractions comprise the historical alpha lipoprotein electrophoretic mobility class.

Although the exact physiological role of HDL is unknown, conventional understanding focuses on its contribution to reverse transport of cholesterol from macrophages to the liver (figure 1).[57] However, minimal data are available in humans to suggest that HDL is mechanistically linked to atherosclerosis, and cardiovascular outcomes; studies investigating HDL-targeted therapies have proved negative.[57,58] Genetic support for these negative findings came from prospective general population cohorts[59] and genetics consortia.[60] Indeed, insights from epidemiological studies indicate a more complex association between HDL cholesterol and risk for cardiovascular events, chronic kidney disease, infection, and premature mortality, which is J-shaped or U-shaped rather than inverse,[61–64] with the nadir range between 1·3 and 2·4 mmol/L (50 and 93 mg/dL), depending on sex, ethnicity, and comorbidities. On the basis of these new data, the contention that HDL cholesterol is a protective factor for the entire population is no longer tenable.

Disorders associated with low HDL cholesterol (hypoalphalipoproteinaemia)

HDL cholesterol typically shows a normal distribution in women and men, with concentrations at the extremes either due to common secondary causes (table 3), polygenic factors,[65] or rare monogenic disorders. In a US study of 258 252 participants referred for lipid testing, 504 (0·2%) participants had HDL cholesterol concentrations of less than 0·52 mmol/L (20 mg/dL), which was attributable to secondary causes in 206 (40%) participants. Among the 201 patients with an identified genetic basis, 14 (7%) were homozygotes, or compound or double heterozygotes (ie, monogenic) while 59 (29%) were heterozygotes for mutations in *APOA1, ABCA1, LCAT*, or *LPL* genes, with a possible polygenic burden in some of the remaining 128 patients (64%).[66]

Pathophysiology

Apolipoprotein A-I deficiency and Tangier disease

Despite similarly low concentrations of HDL cholesterol and apolipoprotein A-I, clinical presentation differs between apolipoprotein A-I deficiency and Tangier disease due to homozygous *ABCA1* mutations, implying discrete and organ-specific effects of ABCA1 on the generation of HDL and cellular cholesterol homoeostasis, which are supported by studies in animal models.[67–69] Although apolipoprotein A-I and ABCA1 in the liver and intestine have a key role in the production of HDL, ABCA1-mediated cholesterol efflux prevents foam cell formation independent of plasma HDL cholesterol concentrations.[70]

Lecithin cholesterol acyltransferase deficiency and fish-eye disease

Familial lecithin cholesterol acyltransferase (LCAT) deficiency is characterised by an absence of LCAT activity and the absence of cholesteryl esters in the plasma; unesterified cholesterol accumulates in plasma as lipoprotein X (LpX), an abnormal cholesterol-rich particle, which is cleared mainly by the reticuloendothelial system of the liver and spleen.[71] In fish-eye disease, LCAT loses

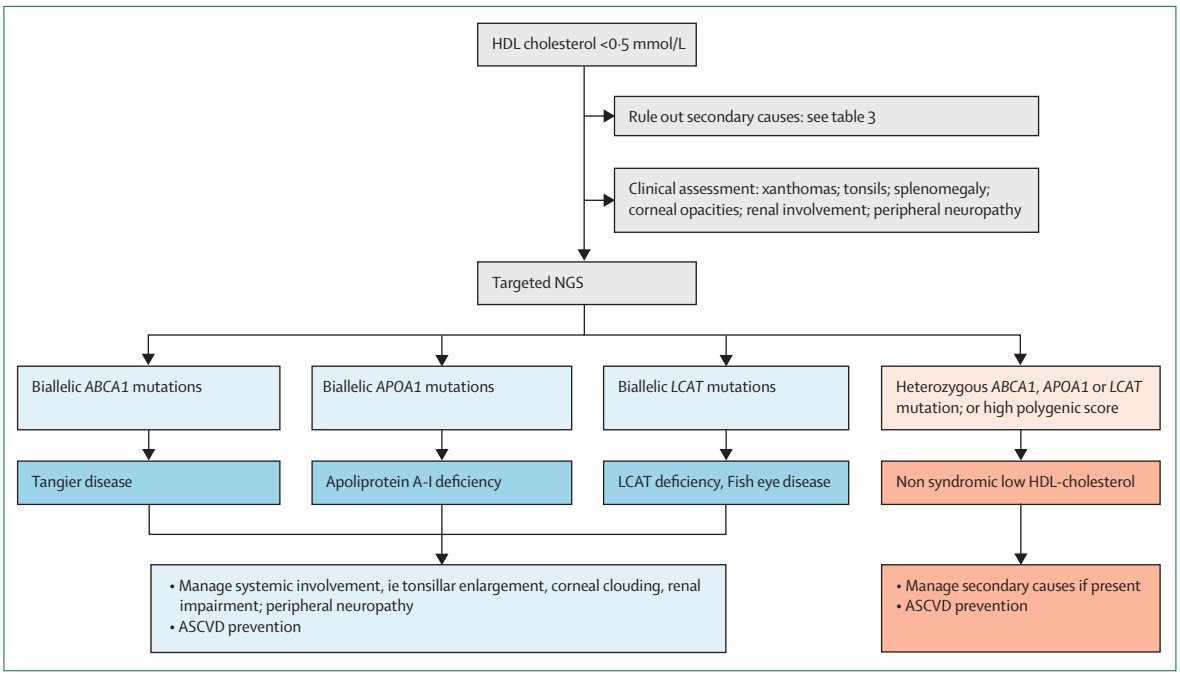


Figure 6: **Algorithm for the diagnosis and management of low HDL cholesterol cholesterol (hypoalphalipoproteinaemia)**
ABCA1=gene encoding ATP-binding cassette protein type A1. *APOA1*=gene encoding apolipoprotein A1. ASCVD=atherosclerotic cardiovascular disease. *LCAT*=gene encoding lecithin cholesterol acyl transferase. NGS=next generation sequencing.

its ability to esterify cholesterol on HDL, but retains its activity on LDL, resulting in subnormal plasma concentrations of cholesteryl ester.[72]

The pathogenesis of the renal disease associated with familial LCAT deficiency is not completely understood but could relate, at least partly, to the accumulation of LpX,[73] which becomes trapped in renal capillaries, inducing endothelial damage and vascular injury.[74] Both familial LCAT deficiency and fish-eye disease present with low plasma HDL cholesterol concentrations and defective reverse cholesterol transport, which might be expected to increase cardiovascular risk. However, atherosclerosis is decreased in familial LCAT deficiency. This decrease could relate to preserved macrophage cholesterol removal and lower LDL cholesterol concentrations in familial LCAT deficiency but not fish-eye disease.[75]

Clinical presentation and diagnosis

Figure 6 provides an algorithm for the diagnosis and management of disorders characterised by very low HDL cholesterol concentrations (ie, <0·5 mmol/L or <20 mg/dL) in the absence of severe hypertriglyceridaemia. Secondary causes should be first excluded before consideration of a genetic cause (table 3). In general, only homozygosity or compound heterozygosity for loss-of-function mutations in rate-limiting genes for HDL biogenesis display clinical manifestations, although there are exceptions.[76] Specific clinical features can provide clues to the underlying molecular diagnosis (figure 2).

APOA1 mutations

More than 60 different missense mutations in *APOA1* have been described, with data from the Copenhagen City Heart Study[77] showing a prevalence of heterozygotes of approximately 2·7 cases per 1000 people. Heterozygotes are typically asymptomatic despite low HDL cholesterol concentrations, although some specific ultrarare missense mutations are the second most frequent cause of familial amyloidosis after transthyretin variants.[76] The location of the structural alteration is reported to determine the site of deposition of apolipoprotein A-I-amyloid; those affecting the amino-terminal domain are mainly associated with hepatic and renal amyloidosis, whereas mutations affecting residues 173–178 are mostly responsible for cardiac, laryngeal, and cutaneous amyloidosis.[76,78] Only some amyloidogenic apolipoprotein A-I variants are associated with low HDL cholesterol concentrations; many of these were initially identified by immunohistochemical analysis of amyloid in affected organs, although definitive diagnosis now requires *APOA1* gene sequencing.[7]

Homozygous or compound heterozygous apolipoprotein A-I deficiency has been described in less than 20 patients worldwide and is characterised by an almost complete deficiency of HDL cholesterol (<0·3 mmol/L or <10 mg/dL) and apolipoprotein A-I (<0·1 g/L) and, in most individuals, premature coronary heart disease.[79–81] Patients with two null alleles have xanthomas, either limited to the eyelids, or covering the body (figure 2).[79–81] Patients with homozygous or hemizygous missense

mutations have residual plasma concentrations of a structurally abnormal apolipoprotein A-I, and can show corneal clouding, similar to familial LCAT deficiency and fish-eye disease.[79–81] However, this feature is inconsistently observed in patients with complete apolipoprotein A-I deficiency, sometimes detectable only by slit lamp examination.[79–81] Definitive diagnosis is made by targeted sequencing of the *APOA1* gene.

Tangier disease due to ABCA1 mutations

More than 170 mutations in *ABCA1* have been described, with an estimated population prevalence of heterozygotes of approximately three cases per 1000 people.[59] Diagnosis of Tangier disease is based on biallelic mutations in *ABCA1*,[7,81–83] resulting in very low plasma concentrations of HDL cholesterol and apolipoprotein A-I; more than 110 cases are described in the literature.[81–83] Clinical presentation is variable and depends on cholesterol accumulation in macrophages in different organs, with common clinical signs including the presence of large yellowish tonsils (figure 2), peripheral neuropathy, splenomegaly, and hepatomegaly.[81–83] Additional laboratory findings include low platelet count, anaemia, moderate hypertriglyceridaemia, and low LDL cholesterol concentrations.[81–83] Whether Tangier disease increases the risk of atherosclerotic cardiovascular disease is controversial. Despite some reports of premature myocardial infarction in individuals aged in their 40s,[81–83] other patients with Tangier disease died in their 60s without evidence of atherosclerosis on autopsy.[84] Furthermore, the broad age distribution and referral bias complicate the attribution of atherosclerotic cardiovascular disease risk; low HDL cholesterol concentrations are not fully explanatory. Whether the specific mutation, additional factors, or the combination of both defines the clinical presentation and disease course is not known. Definitive diagnosis is made by DNA sequence demonstration of biallelic *ABCA1* mutations.

LCAT mutations in familial LCAT deficiency and fish-eye disease

More than 80 *LCAT* gene mutations have been reported,[85] but their population prevalence is unknown. Diagnosis of familial LCAT deficiency and fish-eye disease is based on biochemical parameters and is limited to carriers of two mutant *LCAT* alleles. Both conditions are characterised by very low plasma concentrations of HDL cholesterol, together with low concentrations of LDL cholesterol and apolipoprotein B, especially in familial LCAT deficiency.[81,85] Corneal opacity is common (figure 2), typically first noted during adolescence. Patients with familial LCAT deficiency also frequently have mild chronic normochromic anaemia associated with increased reticulocyte count. Renal disease, mainly characterised by proteinuria and progressive renal insufficiency, is the main cause of morbidity and mortality in patients with familial LCAT deficiency,[81,86,87] although the rate of progression is unpredictable and variable. Definitive diagnosis is made by DNA sequence demonstration of biallelic *LCAT* mutations.

Current and future therapy

There is no specific treatment for apolipoprotein A-I deficiency and Tangier disease; nicotinic acid (niacin) or fibrates will not increase HDL cholesterol concentrations for patients with these diseases.[88] There are minimal options for complications such as peripheral neuropathy. The mainstay of atherosclerotic cardiovascular disease risk management is optimal control of other risk factors, including the use of LDL cholesterol lowering therapies. The infusion of synthetic HDL over 6 months has been tested in 30 patients with apolipoprotein A-I deficiency or Tangier disease; there was no regression of atherosclerosis, as assessed with 3-T MRI.[89]

Similarly, there is no specific therapy for LCAT deficiency syndromes. Treatment with angiotensin converting enzyme inhibitors and angiotensin receptor blockers has been reported to reduce proteinuria and progression of renal disease.[90] Severe renal disease requires haemodialysis and, eventually, kidney transplantation, although the pathology often rapidly reappears.[91] Progression of corneal opacities could require corneal transplantation to restore vision. Novel approaches, such as enzyme replacement therapy with human recombinant LCAT and small molecules enhancing LCAT activity,[92,93] could offer future potential. For example, benefits of human recombinant LCAT infusion on plasma lipids, anaemia, and renal function were reported in one case of familial LCAT deficiency.[94]

Hyperalphalipoproteinaemia

Hyperalphalipoproteinaemia is associated with loss-of-function mutations in *CETP*, encoding cholesteryl ester transfer protein (which mediates the heteroexchange of cholesterol and triglycerides in apolipoprotein B-containing particles and HDL),[57,58] and loss-of-function mutations in *SRB1* (also known as *SCARB1*), encoding scavenger receptor B-I (SR-BI), which is a hepatic receptor that takes up HDL destined for the bile (figure 1). Both are characterised by HDL cholesterol concentrations of greater than 2·6 mmol/L (100 mg/dL).[95–97] Mutations in both genes act co-dominantly, with heterozygotes showing intermediate elevations of HDL cholesterol between wild-type and homozygous individuals. The clinical phenotype and atherosclerotic cardiovascular disease risk are poorly defined for CETP deficiency, and even less is known about SR-BI deficiency, although some patients have adrenal insufficiency and platelet dysfunction,[97,98] and also increased risk of atherosclerotic cardiovascular disease.[98] Clinical trials evaluating the potential of CETP inhibitors for preventing cardiovascular events have been inconclusive.[99] Another rare monogenic cause of hyperalphalipoproteinaemia is hepatic lipase deficiency due to biallelic loss-of-function mutations in the *LIPC* gene, which results in a complex

Panel 3: **Laboratory assessment of patients with rare dyslipidaemias**

Baseline lipid evaluation
- Lipoprotein profile: total, LDL, and HDL cholesterol and triglyceride
- Apolipoproteins B and A-I
- Lipoprotein(a)

Screening for secondary causes of dyslipidaemia
- Diabetes: fasting glucose, HbA_{1c}
- Hypothyroidism: thyroid stimulating hormone
- Liver disease: transaminases, bilirubin, alkaline phosphatase, γ-glutamyl transferase
- Renal disease: serum creatinine, urinary albumin, albumin to creatinine ratio
- Autoimmune diseases: serum rheumatoid factor, antinuclear antigen, C-reactive protein

Associated abnormalities
- Haematological: abnormal erythrocyte morphology in decreased low density lipoprotein cholesterol states and lecithin-cholesterol acyltransferase deficiency
- Coagulation: prolonged international normalised ratio in decreased low density lipoprotein cholesterol states
- Serum fat soluble vitamin concentrations: reduced in decreased LDL cholesterol states
- Serum pancreatic lipase: increased concentrations in hypertriglyceridaemia-associated pancreatitis
- Cardiovascular: non-invasive imaging of premature atherosclerosis in coronary, extracranial carotid arteries, and peripheral arteries in several conditions
- Gastrointestinal and hepatic: abdominal ultrasound for fatty liver in decreased low density lipoprotein cholesterol states, hepatosplenomegaly in monogenic chylomicronaemia
- Ophthalmologic: retinopathy in decreased LDL cholesterol states, corneal opacities in decreased HDL cholesterol states

Diagnostic targeted sequencing panel or exome slice for dyslipidaemia genes
- Causative genes listed in table 2

Specialised research lipid biochemistry (not essential; confirmatory or for academic interest)
- Serum or plasma plant sterols to confirm sitosterolaemia
- Post-heparin plasma lipolytic assay to confirm lipoprotein lipase deficiency
- Serum or plasma lysosomal acid lipase to confirm lysosomal acid lipase deficiency
- Serum cholesterol efflux capacity in HDL cholesterol deficiency states

dyslipidaemia characterised by hypercholesterolaemia and hypertriglyceridaemia, in addition to increased concentration of compositionally abnormal HDL.[100] Some of these patients have an increased risk of atherosclerotic cardiovascular disease, which can be managed with statins. Currently, there are no investigational therapies for hyperalphalipoproteinaemia, instead management is directed towards reducing atherosclerotic cardiovascular disease risk with existing therapies.

Panel 4: **Websites for health professionals, patients, and families**

- National Organization for Rare Diseases; https://rarediseases.org/
- National Institutes of Health Genetics Home Reference; https://ghr.nlm.nih.gov/condition
- Rare Disease Report; https://www.mdmag.com/specialty/rare-diseases
- Orphanet; https://www.orpha.net/consor/cgi-bin/index.php?lng=EN
- Hypercholesterolemia Foundation; https://thefhfoundation.org/
- FH Canada; https://www.fhcanada.net/
- Heart UK; https://www.heartuk.org.uk/

Care pathway

Care for patients with rare dyslipidaemias would be ideally delivered in a specialised centre (eg, where apheresis is available if required). Responsibility for care should fall to an experienced individual, such as a certified lipidologist, endocrinologist, cardiologist, gastroenterologist, or primary care physician. Referral to speci fic subspecialties for baseline assessment and monitoring is appropriate—eg, an ophthalmologist for patients with abetalipoproteinaemia, FHBL, chylomicron retention disease, or fish-eye disease; a neurologist for patients with abetalipoproteinaemia, FHBL, chylomicron retention disease, or Tangier disease; an otolaryngologist for patients with Tangier disease; and a nephrologist for patients with LCAT deficiency. Children should receive care from a pediatrician with dyslipidaemia expertise. Laboratory evaluation of patients with rare dyslipidaemias is shown in panel 3. Websites with information for providers and patients are shown in panel 4.

Conclusion

Advances in genomic research promise future translational benefits of precision medicine in the management of rare lipoprotein disorders. DNA-based diagnoses provide a more expedited path and greater accuracy in these rare disorders than previous diagnostic assays (eg, plasma-based enzymatic or transfer activity assays or ex-vivo cellular functional assessments of receptor activity or of cholesterol efflux). However, with some exceptions (ie, heterozygous and homozygous familial hypercholesterolaemia and monogenic chylomicronaemia) there is no evidence yet that therapeutic decisions are altered or guided by a DNA-based

	Indication	Mechanism of action	Development stage
Lomitapide	Homozygous familial hypercholesterolaemia	Oral MTP inhibitor	Approved in North America, Europe, Latin America, and Asia
Mipomersen	Homozygous familial hypercholesterolaemia	Anti-*APOB* antisense oligonucleotide	Approved in the USA and Japan; sales stopped in the USA in 2018
AAV8.TBG.hLDLR (RGX-501)	Homozygous familial hypercholesterolaemia	*LDLR* gene therapy	Phase 1 and 2
Evinacumab	Homozygous familial hypercholesterolaemia, monogenic chylomicronaemia	Anti-ANGPTL3 antibody	Phase 2 and 3
Alipogene tiparvovec	Monogenic chylomicronaemia	*LPL* gene therapy	Development suspended
Volanesorsen	Monogenic chylomicronaemia	Anti-APOC3 antisense oligonucleotide	Approved in Europe
CSL-112 and CER-001	Low HDL-cholesterol	Synthetic APOA1 infusion	Phase 3
ACP-501	LCAT deficiency	Recombinant LCAT	Phase 1 and 2
Sebelipase alfa	LAL deficiency	LAL replacement	Approved in North America, Europe, Latin America, and Asia

ANGPTL3=angiopoietin-related protein 3. APOA1=apolipoprotein A-I. APOB=apolipoprotein B. APOC3=apolipoprotein C-III. HoFH= homozygous familial hypercholesterolaemia. LAL=lysosomal acid lipase. LCAT=lecithin cholesterol acyl transferase. LDLR=LDR receptor. LPL=lipoprotein lipase. MTP=microsomal triglyceride transfer protein.

Table 4: **Novel therapeutics for selected rare lipid disorders by indication**

diagnosis. Treatment of individuals with these rare conditions is guided largely by clinical and biochemical features, with treatment modalities and approaches based on observational studies in small cohorts of rare individuals and extrapolations from larger clinical trials. New treatments targeted to key molecular pathways have now been approved or are in development for some rare dyslipidaemias (table 4). At present, evidence-based management for these conditions poses a challenge for clinicians because of their infrequency and the interindividual variability in their causes and phenotypic expression. This EAS task force consensus statement addresses these concerns by providing accessible clinical guidance for clinicians that aims to improve diagnosis and initiation of appropriate treatment options.

The task force recognises, however, several unmet needs in this setting, including practical difficulties (relating to technologies, as well as the cost and access to diagnostic modalities and emerging therapies). Key deterrents are the scarcity of information about these disorders, specifically with respect to prevalence, pathophysiology, and outcomes, as well as the absence of effective treatments for specific conditions. Also, third party payers demand prospective data on clinical utility for molecular diagnostics and hard outcomes for new therapies, which are logistically challenging to obtain because the entire global population of individuals with a rare dyslipidaemia could be as low as a few hundred or a few thousand. A potential geopolitical issue is ensuring access to diagnosis and management of these largely autosomal recessive conditions in regions with a high prevalence of consanguinity. The development of collaborative registries, in conjunction with integration of genomic technologies, has the potential to deliver real practical benefit to all stakeholders. These benefits include improvement in awareness, management, and access to effective therapy for these conditions. The pharmaceutical industry could play a key role in the future, working with governments and non-governmental organisations. Together, complementary and coordinated political, economic, and socioeconomic actions, combined with technological advances, could mitigate underdiagnosis and undertreatment, and ultimately transform health policy for the care of patients with rare lipoprotein disorders.

Search strategy and selection criteria

References for this Review were identified through searches of PubMed for articles published from Jan 1, 2000 to June 21, 2019, using search terms "rare lipoprotein disorder", "rare disease", "dyslipidaemia" in combination with the terms "low-density lipoprotein cholesterol", "triglycerides", "high-density lipoprotein cholesterol", "monogenic", "polygenic", "management", and "diagnosis". Relevant articles were also identified through searches of the reference lists of the identified literature. Articles resulting from these searches and relevant references cited in those articles were reviewed. Only articles published in English were included.

Contributors

This task force of the European Atherosclerosis Society was co-chaired by ALC and HNG. The individual sections were drafted by three writing groups, focused on LDL cholesterol (ALC, MAv), JB, MC, FK, KGP, FJR, KKR, JKS, LT); triglyceride (HNG, RAH, MAr, DG,ESS), and HDL (CJB, LC, AvE, RF-S, GKH, DL, ATR). The draft was reviewed by the co-chairs, JB, MJC, and RAH. All authors reviewed and approved the final manuscript before submission.

Declaration of interests

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Diagnostics, and personal honoraria for consultancy from Aegerion, Amgen, Gemphire, and Sanofi. JB has received grants from AstraZeneca and Pfizer, grants and personal honoraria for consultancy from Amgen, NovoNordisk, Regeneron, and Sanofi, and personal honoraria for consultancy from Akcea, Eli Lilly, and Merck. HNG has received grants and personal honoraria for consultancy from Merck, grants from Sanofi-Regeneron, Amgen, Medimmune, and AstraZeneca, and personal honoraria for consultancy from Janssen, Sanofi, Regeneron, Kowa, Pfizer, and Resverlogix. MAr has received grants from Aegerion and Regeneron, grants and personal honoraria for consultancy from Akcea, Ionis, Amgen, Amyrt, and Sanofi, and personal honoraria for consultancy from Alfasigma, Mylan, and Pfizer. MAv has received grants and personal honoraria for consultancy from Aegerion, Akcea, Ionis, Alfasigma, Amgen, Amryt, Pfizer, Regeneron, and Sanofi. CJB has received personal honoraria for consultancy from Amgen. LC has received grants and personal honoraria for consultancy from MedImmune, and grants from Cerenis therapeutics, Daiichi Sankyo, and Alexion Pharma. MJC has received grants from Amgen, Kowa Europe, and Pfizer, and personal honoraria for lectures and speakers bureau from Akcea, Alexion, Amarin, Amgen, Daiichi-Sankyo, Kowa Europe, Merck, MSD, Pfizer, Sanofi, Regeneron, and Unilever. MC has received grants from RegenXBio, Regeneron Pharmaceuticals, and Akcea Therapeutics. DG has received grants and personal honoraria for lectures and speakers bureau or consultancy from Aegerion, Akcea, Amgen, HDL Therapeutics, Ionis Pharmaceuticals, Novartis, Regeneron, and Sanofi, grants from Acasti, AstraZeneca, Boehringer Ingelheim, Canadian Cardiovascular Research Network, Cerenis, Dalcor Pharma, Esperion, Gemphire, GlaxoSmithKline, Institut de cardiologie de Montréal, Ironwood, Kowa, Lilly, Pfizer, The Medicines Company, and UniQure, and personal honoraria for lectures and speakers bureau or consultancy from Nestlé. GKH has received grants from the Netherlands Organisation for Scientific Research, the CardioVascular Research Initiative, and the EU, personal honoraria for consultancy and non-financial support from Amgen, Aegerion, AstraZeneca, and Sanofi, personal honoraria for lectures and speakers bureau or consultancy from Pfizer, Regeneron, Kowa, Ionis Pharmaceuticals, and Cerenis, and non-financial support from Synageva. KGP has received grants and personal honoraria for consultancy from Sanofi, grants from Novartis, and personal honoraria for consultancy from Amgen, MSD, Akcea, Silence Therapeutics, Daiichi Sankyo, and Regeneron. FJR has received personal honoraria for consultancy and non-financial support from Amgen, Sanofi, Regeneron, and The Medicines Company. KKR has received grants and personal honoraria for consultancy, advisory boards, and lectures from Amgen, Sanofi, Regeneron, MSD, and Pfizer, personal honoraria for consultancy, advisory boards, and lectures from AbbVie, AstraZeneca, The Medicines Company, Resverlogix, Akcea, Boehringer Ingelheim, Novo Nordisk, Takeda, Kowa, Algorithm, Cipla, Cerenis, Dr Reddys, Lilly, Zuellig Pharma, Silence Theapeutics, and Bayer. ESS has received personal honoraria for lectures and speakers bureau from Amgen, Sanofi, Akcea, and Novartis. LT has received personal honoraria for lectures and speakers bureau or consultancy from MSD, Sanofi, Amgen, Abbott, Mylan, Bayer, Actelion, Novartis, Astra, Recordati, Pfizer, Servier, and Novo Nordisk. She is also the President, of the European Atherosclerosis Society and an editorial board member of the European Heart Journal. ALC has received grants from Pfizer, Sanofi, Regeneron, Merck, and Mediolanum, non-financial support from SigmaTau, Menarini, Kowa, Recordati, and Eli Lilly, and personal honoraria for lectures and speakers bureau or consultancy from AstraZeneca, Genzyme, Menarini, Kowa, El Lilly, Recordati, Pfizer, Sanofi, Mediolanum, Pfizer, Merck, Sanofi, Aegerion, and Amgen. All other authors declare no competing interests.

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