Rare Dyslipidaemias: From Phenotype to Genotype to Management. A European Atherosclerosis Society Task Force Consensus Statement.

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Rare Dyslipidaemias: From Phenotype to Genotype to Management. A European Atherosclerosis Society Task Force Consensus Statement.

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Abstract

Genome sequencing and gene-based therapies appear poised to advance the management of rare lipoprotein disorders and the associated dyslipidaemias. In practice, however, underdiagnosis and undertreatment are common, in large part due to interindividual variability in the genetic aetiology and phenotypic presentation of these conditions. To address these challenges, this Task Force from the European Atherosclerosis Society provides practical clinical guidance focusing on patients with extreme levels (either low or high) of plasma low-density lipoprotein cholesterol, or triglycerides, or high-density lipoprotein cholesterol. The Task Force also recognises the lack 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.

Key words: rare lipoprotein disorder; rare disease; dyslipidaemia; clinical guidance; LDL cholesterol; triglycerides; chylomicronaemia; HDL cholesterol; familial hypercholesterolaemia; abetalipoproteinaemia; hypobetalipoproteinaemia; hypertriglyceridaemia; monogenic; polygenic; management; diagnosis; premature atherosclerosis; pancreatitis
Introduction

What is a rare disease? Although universal definition is elusive, the average global prevalence threshold for a rare disease is estimated at 40 to 50 cases/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 >7000 rare diseases identified to date, as many as one in 12 people, or \(~ 36\) million people in Europe and perhaps 500 million 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 odyssey before the correct diagnosis is made.\(^5\) As over 80% of rare diseases have a genetic aetiology, genomic analysis plays a critical role in diagnosis, management and driving development of novel treatments.

Progress in the rare dyslipidaemia field, together with decreasing cost of genome sequencing and bioinformatics, seems to argue for a precision medicine approach to the management of rare dyslipidaemias. Yet the reality for clinical practice often trails behind. Several factors may explain this, including the lack 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, recognition that small-effect genetic variants may collectively influence phenotypic expression under a polygenic framework provides further diagnostic challenges.\(^6\) All these factors create impediments to diagnosis, management, and access to treatments.

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, as well as practical clinical guidance for rare lipoprotein disorders associated with extreme levels (either low or high) of low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C). While genetic testing has a clear role in definitive diagnosis, it is predominantly the phenotypic expression that determines clinical management.

Search strategy

References were identified through searches of PubMed for articles published from 2000, by the use of the 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.
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, co-dominant, or recessive inheritance. These 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 "pan dyslipidaemia" panels and defines bioinformatic parameters to highlight variant profiles from whole genome or exome sequencing results. Mutations in different genes may occasionally produce an identical phenotype (e.g. in dominant forms of familial hypercholesterolaemia), while in other cases contrasting mutations (i.e. loss-of-function versus gain-of-function) within the same gene may cause opposite phenotypes (e.g. mutations in APOB and PCSK9 causing either high or low LDL-C). A schematic overview of lipoprotein metabolism focusing on gene products causing monogenic dyslipidaemias is provided in Figure 1.

LDL-related disorders

Apolipoprotein (apo) B-containing lipoproteins comprise LDL, intermediate-density lipoproteins (IDL), very low-density lipoproteins (VLDL), chylomicrons and their remnant particles, intermediate density lipoproteins (IDL) corresponding to the remnants of VLDL particles, and lipoprotein (a). All are pro-atherogenic and play key roles in the transport of cholesterol and TG in the circulation. These particles comprise approximately the historic “beta and pre beta lipoprotein” electrophoretic mobility class.

Disorders characterised by very high LDL-C levels

Pathophysiology

Hyperbetalipoproteinaemia is characteristic of several rare dyslipidaemias with markedly elevated LDL-C levels or apo B-100 levels as the defining feature; it predominantly results from impairment of the interaction between the LDL particle and the LDL receptor. The resulting clinical disorder is familial hypercholesterolaemia (FH), in which the core defect is delayed clearance of LDL from the plasma, resulting in hypercholesterolaemia, physical signs (Figure 2) and, if untreated, premature atherosclerotic cardiovascular disease (ASCVD).

There are numerous comprehensive reviews on the diagnosis and management of FH. Heterozygous FH (HeFH) is the most common inherited metabolic disorder causing ASCVD, affecting 1:200-250 individuals. Because HeFH is not a rare disorder, we do not deal with it here in depth. In contrast, homozygous FH (HoFH) is a very rare disease thought to affect about 1:160,000 - 300,000 people.

FH is an autosomal co-dominant disorder. Most individuals with genetically confirmed HeFH and HoFH 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 <10% of HeFH cases, and two mutant alleles of these genes and of LDLRAP1 (also called ARH - autosomal recessive hypercholesterolaemia), produce a phenotype resembling HoFH.
More than 2,300 unique FH-causing mutations have been reported in the **LDLR** gene. Of the **APOB** mutations, p.R3527Q (arginine to glutamine at residue 3527), is the most frequently observed, and disrupts the interaction of apo B with the LDL receptor. About 50 additional likely pathogenic **APOB** mutations are associated with hyperlipidaemia, many involving arginine residues within the receptor-binding domain encoded mainly by exon 26. More than 30 gain-of-function mutations in the gene encoding proprotein convertase subtilisin/kexin type 9 (PCSK9) have been reported in FH patients; together these account for <1% of all FH cases. Until more consistent data emerge, we do not consider ultrarare STAP1 gene mutations to cause FH. Finally, at least 20% of patients referred to a lipid clinic with suspected HeFH carry polygenic susceptibility to high LDL-C. Detailed discussion of polygenic aetiologies of dyslipidaemias is beyond the scope of this statement; the interested reader can access recent reviews on this topic.

**Clinical presentation and diagnosis**

Given the remit of this statement, we focus on very rare patients with extremely elevated LDL-C levels, essentially HoFH (Figure 3). Historically, a treated LDL-C >8 mmol/L (>300 mg/dL) or untreated LDL-C >10 mmol/L (>400 mg/dL), together with the presence of cutaneous or tendon xanthomas before the age of 10 years, was considered diagnostic of HoFH, although it is now recognised that clinical presentation may vary, in large part due to the genetic heterogeneity of FH. Diagnosis still primarily depends on clinical assessment; scoring systems can be helpful, as can targeted DNA sequencing when biallelic pathogenic mutations are shown in known causative genes. HoFH patients 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). The severity of the plasma LDL-C elevation and clinical features depend both on the underlying causative gene and the type of mutation, although there is considerable inter-individual variability. Since the individual LDL-C level rather than mutation type is the key determinant of the ASCVD risk, treatment intensity should be tailored accordingly.

Other rare dyslipidaemias may have a clinical presentation similar to HoFH, albeit usually with lower LDL-C levels (Figure 3). Beta-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, results in retention of non-cholesterol sterols, and is characterised by atypical xanthomatosis with elevated levels of plant sterols and stanols (phytosterols) with and without elevated LDL-C levels, and with variable susceptibility to early ASCVD (Figure 2H). Very occasionally, some milder cases of elevated LDL-C together with hepatosplenomegaly and variable TG levels result from lysosomal acid lipase deficiency (LALD, also called cholesterol ester storage disease or, in paediatric patients, Wolman disease), an autosomal recessive disorder in the **LIPA** gene. Definitive diagnosis for these other rare conditions is by DNA sequencing.

**Current and future therapy**

Management of HoFH builds on algorithms for HeFH that are well established and typically involve the combination of maximally tolerated statin, ezetimibe, and a PCSK9 inhibitor, in addition to diet and lifestyle. Moreover, for HoFH, lipoprotein apheresis is considered as foundational, given the severity of LDL-C elevation, profound atherosclerosis risk and refractoriness to other treatments. Treatment
in HoFH can be guided by genetic testing as 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 bi-allelic gain-of-function PCSK9 mutations are present (Figure 3). The oral MTP inhibitor lomitapide is another adjunctive therapeutic option in HoFH patients; the effectiveness of this treatment is maximised with adherence to a low-fat diet (<20% of energy from fat) with dosing outside of mealtimes to minimise gastrointestinal symptoms; however, hepatic steatosis is often seen. Mipomersen, a second-generation apo B antisense oligonucleotide, is available in the USA as part of a Risk Evaluation and Mitigation Strategies programme due to severe adverse effects, including elevated liver transaminases and fatty liver disease. Mipomersen is not licensed in Europe. Evinacumab, a monoclonal antibody to ANGPTL3, and LDLR gene therapy may offer future therapeutic potential as adjunctive therapies. Rarely, liver transplantation in HoFH patients may be considered. If sitosterolaemia is diagnosed, the treatment is markedly different: plasmapheresis is not required, and the hyperlipidaemia often responds well if dietary sterol intake is reduced, and to treatment with ezetimibe or bile acid sequestrants. If LALD is diagnosed, treatment includes enzyme replacement by infusion of sebelipase alfa.

Management of people with HoFH merits consideration of a wide range of other issues relating to genetic counselling, cascade screening to identify family members affected with heterozygous FH and, in female patients, contraception and pregnancy. Readers are referred to recent reviews.

**Disorders characterised by very low LDL-C levels**

Primary hypobetalipoproteinaemia refers to a group of inherited dyslipidaemias characterised by very low or absent plasma LDL-C and apo B levels. Other lipids and lipoproteins can also be involved, depending on the specific gene and severity of the mutation(s) (Table 2).

**Pathophysiology**

Hypobetalipoproteinaemia can result from decreased production or increased catabolism of apo B-containing lipoproteins. Loss-of-function (LOF) mutations in the MTP gene cause abetalipoproteinaemia (ABL; also called Bassen–Kornzweig syndrome), an autosomal recessive disorder characterised by the absence of VLDL and chylomicron production, conferring undetectable plasma levels of LDL-C and apo B, and very low TG and total cholesterol (<0.33 mmol/L or 30 mg/dL). To date, over 30 different LOF mutations in the MTP gene have been described, all of which ultimately impair the ability to lipidate nascent apo B-containing lipoproteins.

Homozogous familial hypobetalipoproteinaemia (FHBL) clinically resembles ABL. An autosomal co-dominant disorder involving the APOB gene, FHBL is characterised by very low levels of apo B (<5th percentile for age and sex) and LDL-C (usually <1.0 mmol/L or <38.7 mg/dL). 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, i.e. FH. 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 apo B (i.e. apo B-9 to apo-B-89, corresponding to 9%
to 89% of the full length protein, respectively), decreased secretion of VLDL, and increased catabolism of VLDL and LDL, resulting in reductions in circulating levels of cholesterol and TG.\textsuperscript{30-32} Other causes of primary hypobetalipoproteinaemia include LOF mutations in \textit{SAR1B}, the gene encoding Sar1 homolog B GTPase, \textit{ANGPTL3} encoding ANGPTL3 and \textit{PCSK9}. Biallelic mutations in \textit{SAR1B} cause autosomal recessive chylomicron retention disease (CRD, also known as Anderson disease), which is characterised by failure of chylomicron secretion from enterocytes.\textsuperscript{33} In contrast, LOF mutations in \textit{ANGPTL3} cause familial combined hypolipidaemia although the mechanism is incompletely understood (\textbf{Table 2}).\textsuperscript{34,35} In addition, over 30 different LOF mutations in \textit{PCSK9} result in reduced lysosomal degradation of the LDL receptor, with increased recycling to the cell surface which drives increased catabolism of LDL particles, reducing LDL-C levels.\textsuperscript{15}

\textbf{Clinical presentation and diagnosis}

\textit{Figure 4} provides an algorithm for the diagnosis and management of disorders characterised by very low LDL-C levels. ABL and homozygous FHBL are associated with undetectable levels of LDL-C and of apo B on direct assay; TG is very low and almost all plasma cholesterol is carried by HDL particles. Because exogenous fat-soluble vitamins are absorbed via chylomicrons and transported via apo B-containing lipoproteins, the defects in ABL, homozygous FHBL, and CRD lead to severe fat-soluble vitamin deficiencies. Clinical manifestations (\textbf{Figures 2I-K}) 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).\textsuperscript{28,29,33} There have been rare reports of hepatic steatosis progressing to hepatic fibrosis in these conditions. A differentiating feature is that obligate heterozygote parents of homozygous FHBL patients have depressed LDL-C levels, whereas parents of ABL patients have normal lipid profiles. Heterozygous HBL patients also have increased risk of hepatic steatosis, but concurrently reduced risk of ASCVD.\textsuperscript{28}

CRD may be considered if there is failure to thrive in infancy, together with severe malabsorption with steatorrhea, and fat soluble vitamin deficiency.\textsuperscript{33} CRD is characterised by relatively normal TG levels, with absence of apo B-48 and chylomicrons after a fat load, and less severe eye involvement than in ABL. Obligate heterozygote parents of CRD children have normal lipid profiles. In contrast, in heterozygotes for \textit{ANGPTL3} deficiency, levels of total cholesterol, LDL-C, and TG are \textasciitilde 50% of normal with relatively normal HDL-C, whereas homozygotes have very depressed levels of total cholesterol, LDL-C, TG, and HDL-C, albeit without associated vitamin deficiencies or other specific clinical manifestations, and likely protection from ASCVD.\textsuperscript{34,35} Individuals with biallelic \textit{PCSK9} LOF mutations have LDL-C levels that are less severely depressed than in ABL, homozygous FHBL, or CRD; these individuals have no deleterious clinical phenotype.\textsuperscript{36} Diagnosis is confirmed when pathogenic mutations are detected by DNA sequencing.\textsuperscript{15} During the work-up of patients with hypobetalipoproteinaemia, secondary causes such as chronic liver disease, chronic pancreatitis, cystic fibrosis, end-stage renal disease, hyperthyroidism, cachexia and malabsorption, should be excluded (\textbf{Figure 4}).\textsuperscript{26,27}

\textit{Current therapy}
Early diagnosis and treatment are essential to prevent long term ophthalmologic and neurologic complications in ABL, homozygous FHBL and CRD. The overall principles of management for these three conditions include fat-restricted diet (with or without medium chain TG), 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 TG pathway via the portal vein.\(^{26-29}\) No specific management is required for carriers of bi-allelic LOF 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). Subjects carrying a heterozygous LOF mutation in APOB frequently show 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 potential deficiencies may be recommended. Conversely, hypobetalipoproteinaemia associated with ANGPTL3 or PCSK9 LOF mutations appears to represent a benign or even a protective condition; specific treatment is not required.

**Chylomicronaemia syndromes**

Hypertriglyceridaemia (HTG) has been defined as fasting TG >2.0 mmol/L or >180 mg/dL (although some consider the threshold to be >1.7 mmol/L or >150 mg/dL). Severe HTG, defined as TG >10 mmol/L (>885 mg/dL), affects 0.1–0.2% of the population. Fasting TG levels elevated 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 TG levels and/or heterozygous rare incompletely penetrant LOF mutation(s).\(^39\) At most, 1–2% of adults with severe HTG have a monogenic cause, defined as recessive (biallelic) rare large effect variants (i.e. either simple homozygosity or compound heterozygosity), in genes involved in regulating TG-rich lipoprotein metabolism\(^39\). The widely used term “familial chylomicronaemia syndrome” is synonymous with our preferred term of "monogenic chylomicronaemia". Notably, compared to those with much more prevalent multifactorial or polygenic chylomicronaemia, individuals with monogenic chylomicronaemia 1) tend to express their HTG phenotype at younger ages, including childhood; 2) are less likely obese or have secondary factors; 3) can attain fasting TG levels in excess of 20 mmol/L (1780 mg/dL); 4) have a higher lifetime risk of developing acute pancreatitis (i.e. up to 60-70% vs 5-10% in multifactorial chylomicronaemia); 5) have much lower apo B-100 levels; and 6) are very resistant to current TG-lowering medications. **Pathophysiology**

While hepatic overproduction of VLDL is the most common cause of mild to moderate HTG, monogenic severe HTG instead results from severely or completely impaired LPL-mediated lipolysis of TG-rich lipoproteins, particularly large chylomicrons carrying enormous amounts of TG. Chylomicrons are secreted by intestine after consumption of a fat-containing meal and cleared from the circulation after 4-6 hours so that they cannot be detected in the fasting state. Specifically, rare biallelic LOF 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** and discussed below.
Monogenic chylomicronaemia syndrome
To date, biallelic LOF mutations in five genes involved in the catabolism of chylomicron TG, i.e. LPL, APOC2, APOA5, LMF1, and GPIHBP1, encoding LPL, apo C-II, apo A-V, lipase maturation factor 1 (LMF1), and glycosylphosphatidylinositol-anchored HDL-binding protein 1 (GPIHBP1), respectively, cause monogenic chylomicronaemia. All these gene products are required for LPL-mediated lipolysis of chylomicrons and VLDL; however, VLDL levels can be normal or low because VLDL secretion is driven largely by TG brought to the liver by chylomicron remnants. VLDL secretion can be increased if the metabolic syndrome (central obesity, insulin resistance, diabetes) is also present. More than 80% of individuals with monogenic chylomicronaemia have biallelic LPL mutations, of which >100 have been identified.

Apo C-II is the required co-activator of LPL. While biallelic LOF 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. Similarly rare is the complete absence of apo A-V, which is thought to facilitate the interaction of chylomicrons and VLDL with LPL at the surface of the capillary endothelium. Biallelic LOF mutations in APOA5 are seen in 2–5% of individuals with monogenic chylomicronaemia, who can present with a phenotype similar to LPL deficiency, although 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. LMF1 deficiency leads to markedly reduced LPL secretion, causing severe HTG similar to LPL deficiency. Patients with biallelic mutations in LMF1 represent 1–2% of all monogenic severe HTG.

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

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

Other proposed monogenic causes of severe HTG
Complete loss of GPD1 (glycerol-3-phosphate dehydrogenase 1) has been reported in transient childhood HTG, and probably results from increased hepatic secretion of VLDL TG rather than chylomicrons. Other genes with large effect mutations contributing to severe HTG include CREBH, encoding transcription factor cyclic AMP-responsive element-binding protein H, and GCKR, encoding glucokinase regulatory protein. Rare heterozygous LOF variants in these genes contribute to polygenic susceptibility, as described below. Finally, severe HTG is a secondary feature of rare monogenic forms of insulin resistance or diabetes, including familial generalized or partial lipodystrophies.

Polygenic or multifactorial chylomicronaemia
Many clinicians believe that patients with severe HTG must have a monogenic condition. However, severe HTG is most often due to polygenic susceptibility interacting with secondary non-genetic factors.\textsuperscript{6} For example, in a recent study of 573 patients with TG >885 mmol/L, only 1·1% had biallelic mutations in monogenic chylomicronaemia genes, while 14% were heterozygous carriers of a LOF mutation in one of these genes versus only 3·8% of normolipidaemic people.\textsuperscript{39} An even larger number of severe HTG patients has an excessive burden of common DNA polymorphisms, each of which raises TG levels by only a fraction of a mmol/L. By chance, some individuals inherit a preponderance of TG-raising polymorphisms, which cumulatively increase the risk of developing severe HTG. For example, in the patients with severe HTG discussed above, 32% had an extreme accumulation of 32 TG-raising common variants versus 9·5% in controls.\textsuperscript{39} This 3-fold increased susceptibility to HTG is typical for a polygenic trait; the disease risk in genetically predisposed people is increased, but not absolute, since a fraction of healthy controls also carry the same genotypic burden. Secondary factors are frequently present in genetically predisposed individuals who express HTG.

**Clinical presentation**

Clinical features associated with chylomicronaemia are summarised in **Box 1** and **Figure 2L-N**. Severe HTG caused by monogenic LOF 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\textsuperscript{38}. A lipoaemic blood sample will indicate the presence of HTG-induced acute pancreatitis\textsuperscript{38}. In older adolescents and adults who have avoided early-onset pancreatitis, diagnosis may be made during routine blood testing for other reasons. Acute pancreatitis can affect any patient with TG >10 mmol/L (875 mg/dL); however HTG-induced pancreatitis is much more often seen with common multifactorial or polygenic chylomicronaemia\textsuperscript{48}. Whatever the genetic basis, the severity of HTG 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 such as steroids\textsuperscript{38}. Because both parents will be obligate heterozygotes for any of these genes, screening of siblings of an affected child is obligatory; one-quarter of siblings will also have biallelic or homozygous mutations. The lipid phenotype in heterozygous parents or siblings can vary from normal to severe HTG, as discussed above\textsuperscript{39}.

**Diagnosis and treatment**

Diagnosis of monogenic chylomicronaemia should be considered when plasma TG levels are >10 mmol/L (>875 mg/dL), especially when TG far exceed this level (**Figure 5**). As mentioned, most patients with such TG levels have multifactorial or polygenic chylomicronaemia; the proportion with monogenic chylomicronaemia may only be 1-2%\textsuperscript{39}. The absence of secondary factors, and diagnosis at a very early age are suggestive of monogenic chylomicronaemia, particularly if HTG is associated with pancreatitis\textsuperscript{48}. Low plasma levels of plasma apo B (<0.75 g/L) may help differentiate patients with monogenic versus multifactorial chylomicronaemia\textsuperscript{48}. A history of severe HTG in a sibling also suggests a strong genetic basis for this disorder. Clearly, however, differentiating monogenic severe HTG from other more complex aetiologies, such as the combination of heterozygous plus polygenic predisposition, is key\textsuperscript{39,48}. Genetic testing for the five genes involved in LPL-mediated lipolysis plus a polygenic score for HTG may be useful to clarify the genetic basis.\textsuperscript{7}
Therapy centres upon consumption of a low-fat diet, with ideally < 10% of calories from fat (Box 2); 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 avoiding increases in plasma TG levels. 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 demonstrated to reduce VLDL and possibly chylomicron secretion, can also be effective in individuals with polygenic HTG, and the small quantity of added dietary fat is offset by the potential efficacy of this therapy.

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

The limitations of available treatments are clear; typically, patients with monogenic chylomicronaemia have TG levels >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 biologic agents that reduce apo C-III or ANGPTL3, offer the possibility of reducing plasma TG dramatically in individuals lacking LPL activity from monogenic causes. Concerns regarding thrombocytopenia associated with treatment involving the original anti-APOC3 antisense agent volanesorsen in monogenic chylomicronaemia are mitigated somewhat by a next-generation anti-APOC3 agent. Nonetheless, volanesorsen has been recently approved for use in Europe. LPL gene therapy (alipogene tiparvovec) was approved for use in Europe, but the sponsor did not renew the license after 2017.

**Dysbetalipoproteinaemia**

Dysbetalipoproteinaemia (formerly known as broad beta disease or hyperlipoproteinaemia type 3) affects 1 to 2 in 20000 people. Both TG and cholesterol are variably elevated due to pathological accumulation of IDL or VLDL remnants. While it biochemically resembles mixed dyslipidaemia, it can be distinguished by measuring apo B levels. 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 E2 isoform, which has defective binding to the LDL receptor, leading to accumulation of apo 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 polygenic susceptibility factors, including insulin resistance or diabetes, are required together with secondary non-genetic factors such as exogenous hormones, poor diet, hypothyroidism, renal
disease, diabetes, paraproteinaemia or systemic lupus erythematosus. Treatment includes control of secondary factors and use of either statin or fibrate therapy or both.

**Monogenic hypotriglyceridaemia**

There are no reported single gene disorders that lower TG exclusively; this biochemical feature is typically a component of multiscystem conditions characterised by low to absent apo B-containing lipoproteins as discussed above, such as ABL, FHBL and ANGPTL3 deficiency. APOC3 deficiency is associated with reduced TG and increased HDL-C, with reduced ASCVD risk. The reduced TG levels in these conditions have minimal to no clinical consequences per se; treatment should follow the general recommendations for these disorders as discussed above.

**HDL-related disorders**

Plasma levels of HDL-C are routinely measured in a lipid panel for two main reasons: 1) to estimate LDL-C levels in the absence of direct measurement, and 2) to estimate cardiovascular disease risk, given evidence from epidemiologic studies that low HDL-C levels are associated with increased risk for ASCVD. HDL fractions comprise approximately the historic “alpha lipoprotein” electrophoretic mobility class.

While the exact physiologic role of HDL is unknown, conventional understanding focuses on its contribution to reverse transport of cholesterol from macrophages to the liver (Figure 1). There are, however, limited data in humans that HDL is mechanistically linked to atherosclerosis, and cardiovascular outcomes studies investigating HDL-targeted therapies have proved negative. Genetic support for these negative findings came from prospective general population cohorts and genetics consortia. Indeed, recent insights from epidemiological studies and registries indicate a more complex association between HDL-C and risk for cardiovascular events, chronic kidney disease, infection, and premature mortality, that is J-shaped rather than inverse, with the nadir range between 1.3 and 2.4 mmol/L (50 and 93 mg/dL), depending on gender, ethnicity, and comorbidities. Based on these new data, the contention that HDL-C is a protective factor for the entire population is no longer tenable.

**Disorders associated with low HDL-C (hypoalphalipoproteinaemia)**

HDL-C typically shows a normal distribution in women and men, with levels at the extremes either due to common secondary causes (Table 3), polygenic factors or more rare monogenic disorders. In a recent US study of 258,252 subjects referred for lipid testing, 504 (0.2%) had HDL-C levels <0.52 mmol/L (20 mg/dL), which was attributable to secondary causes in 60%, a genetic basis in 14% - 14 were homozygotes, compound or double heterozygotes (i.e. monogenic) and 59 were heterozygotes for mutations in APOA1, ABCA1, LCAT, or LPL genes and a possible polygenic burden in the remainder.

**Pathophysiology**
Apo A-I deficiency and Tangier disease

Despite similarly low levels of HDL-C and apo A-I, clinical presentation differs between apo 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 homeostasis, which are supported by studies in animal models. While apo 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-C levels.

Lecithin cholesterol acyltransferase (LCAT) deficiency and fish-eye disease (FED)

Familial LCAT deficiency (FLD) is characterised by a complete lack 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. In FED, LCAT loses its ability to esterify cholesterol on HDL but retains its activity on LDL, resulting in subnormal plasma levels of cholesteryl ester.

The pathogenesis of the renal disease associated with FLD is not completely understood but may relate, at least partly, to accumulation of LpX, which becomes trapped in renal capillaries, inducing endothelial damage and vascular injury. Both FLD and FED present with low plasma HDL-C levels and defective reverse cholesterol transport, which might be expected to increase cardiovascular risk; however, atherosclerosis is decreased in FLD. This may relate to preserved macrophage cholesterol removal and lower LDL-C levels in FLD but not FED.

Clinical presentation and diagnosis

Figure 6 provides an algorithm for the diagnosis and management of disorders characterised by very low HDL-C levels (i.e. <0.5 mmol/L or <20 mg/dL) in the absence of severe HTG. Secondary causes should be first excluded before consideration of a genetic aetiology (Table 3). In general, only homozygosity or compound heterozygosity for LOF mutations in rate limiting genes for HDL-biogenesis display clinical manifestations, although there are exceptions. Certain clinical features can provide clues to the underlying molecular diagnosis (Figure 2, O-W).

APOA1 mutations

More than 60 different missense mutations in APOA1 have been described, with data from the Copenhagen City Heart Study showing a prevalence of heterozygotes of ~2.7 in 1000. Heterozygotes are typically asymptomatic despite low HDL-C levels, although some specific ultrarare missense mutations are the second most frequent cause of familial amyloidosis after transthyretin (TTR) variants. The location of the structural alteration appears to determine the site of deposition of apo A-I-amyloid; those affecting the amino-terminal domain are mainly associated with hepatic and renal amyloidosis, whereas mutations affecting residues 173 to 178 are mostly responsible for cardiac, laryngeal, and cutaneous amyloidosis. Only some amyloidogenic apo A-I variants are associated with low HDL-C levels; many of these were initially identified by immunohistochemical analysis of amyloid in affected organs, although definitive diagnosis now requires APOA1 gene sequencing.
Homozygous or compound heterozygous apo A-I deficiency has been described in < 20 patients and is characterised by virtually complete deficiency of HDL-C (<0.3 mmol/L or 10 mg/dL) and apo A-I (<0.1 g/L) and, in most individuals, premature coronary heart disease. Patients with two null alleles have xanthomas, either limited to the eyelids, or covering the body (Figure 2, O-Q). Patients with homozygous or hemizygous missense mutations have residual plasma levels of a structurally abnormal apo A-I, and may exhibit corneal clouding, similar to FLD and FED, however, this is inconsistently observed in patients with complete apo A-I deficiency, sometimes detectable only by slit lamp examination. 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 ~3 in 1000. Diagnosis of Tangier disease is based on biallelic mutations in ABCA1, resulting in very low plasma levels of HDL-C and apo A-I; about 110 cases are described in the literature. 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, R-T), peripheral neuropathy, splenomegaly, and hepatomegaly. Additional laboratory findings include low platelet count, anaemia, moderate HTG, and low LDL-C levels. Whether Tangier disease increases the risk of ASCVD is controversial; despite some reports of premature myocardial infarction among individuals in their forties, other Tangier disease patients died in their sixties without evidence of atherosclerosis on autopsy. Furthermore, the broad age distribution and referral bias complicate the attribution of ASCVD risk; low HDL-C levels are not fully explanatory. It is not known whether the specific mutation, additional factors, or the combination defines the clinical presentation and disease course. Definitive diagnosis is made by DNA sequence demonstration of biallelic ABCA1 mutations.

LCAT mutations in FLD and FED

More than 80 LCAT gene mutations have been reported, but their population prevalence, is unknown. Diagnosis of FLD and FED is based on biochemical parameters and is limited to carriers of two mutant LCAT alleles. Both conditions are characterised by very low plasma levels of HDL-C, together with low LDL-C and apo B levels, especially in FLD. Corneal opacity is common (Figure 2, U-W), typically first noted during adolescence. FLD patients also frequently exhibit a 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 FLD patients, 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 apo A-I deficiency and Tangier disease; nicotinic acid (niacin) or fibrates will not increase HDL-C levels in these patients. There are minimal options for complications such as peripheral neuropathy. The mainstay of ASCVD risk management is optimal control of other risk factors, including the use of LDL-C lowering therapies. The infusion of synthetic HDL over 6 months has been tested in 30 patients with apo A-I deficiency or Tangier disease; there was no regression of atherosclerosis, as assessed with 3-T magnetic resonance imaging.
Similarly, there is no specific therapy for LCAT deficiency syndromes. Treatment with angiotensin converting enzyme inhibitors/angiotensin receptor blockers has been reported to reduce proteinuria and progression of renal disease.\textsuperscript{90} Severe renal disease requires haemodialysis and eventually, kidney transplantation, although the pathology often rapidly reappears.\textsuperscript{91} Progression of corneal opacities may require corneal transplantation to restore vision. Novel approaches, such as enzyme replacement therapy with human recombinant LCAT and small molecules enhancing LCAT activity,\textsuperscript{92,93} may offer future potential; benefits of human recombinant LCAT infusion on plasma lipids, anaemia, and renal function were reported in one FLD case.\textsuperscript{94}

**Hyperalphalipoproteinaemia**

Hyperalphalipoproteinaemia is associated with LOF mutations in \textit{CETP}, encoding cholesteryl ester transfer protein, which mediates the heteroexchange of cholesterol and TG in apo B-containing particles and HDL,\textsuperscript{57,58} and LOF mutations in \textit{SRB1} (also known as \textit{SCARB1}), encoding scavenger receptor B-I, a hepatic receptor that takes up HDL destined for the bile (Figure 1). Both are characterised by HDL-C levels $>2.6$ mmol/L (100 mg/dL).\textsuperscript{95-97} Mutations in both genes act co-dominantly, with heterozygotes showing intermediate elevations of HDL-C between wild-type individuals and homozygotes. The clinical phenotype and ASCVD 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,\textsuperscript{97,98} and also increased risk of ASCVD.\textsuperscript{98} Clinical trials evaluating the potential of CETP inhibitors for preventing cardiovascular events have been inconclusive.\textsuperscript{99} Another rare monogenic cause of hyperalphalipoproteinaemia is hepatic lipase deficiency due to biallelic LOF mutations in the \textit{LIPC} gene, which results in a complex dyslipidaemia characterised by hypercholesterolaemia and hypertriglyceridaemia in addition to elevated concentration of compositionally abnormal HDL;\textsuperscript{100} some of these patients have elevated ASCVD risk, which can be managed with statins. Currently, there are no investigational therapies for hyperalphalipoproteinaemia; management is directed towards reducing ASCVD risk with existing therapies.

**Care pathway**

Care for patients with rare dyslipidaemias would be ideally delivered in a specialized centre, e.g. one where apheresis is available if required. Responsibility for care should fall to an experienced individual, who could be a certified lipidologist, endocrinologist, cardiologist, gastroenterologist or primary care physician. Referral to specific subspecialties for baseline assessment and monitoring is appropriate, e.g. an ophthalmologist for ABL, FHBL, CRD or FED, a neurologist for ABL, FHBL, CRD or Tangier disease, an otolaryngologist for Tangier disease, and a nephrologist for LCAT deficiency. Children should receive care from a pediatrician with dyslipidaemia expertise. Laboratory evaluation of patients with rare dyslipidaemias is shown in Box 3. Websites with information for providers and patients are listed at the end of the article.

**Conclusions: Unmet needs and future directions**

Advances in genomic research promise future translational benefits of precision medicine in the management of rare lipoprotein disorders. DNA-based diagnosis provides a more expedited path and...
greater accuracy in these rare disorders than previous diagnostic assays, such as plasma-based enzymatic or transfer activity assays or ex vivo cellular functional assessments of receptor activity or cholesterol efflux. However, with some exceptions, i.e. heterozygous and homozygous FH and monogenic chylomicronaemia, there is no evidence yet that therapeutic decisions are altered or guided by a DNA-based diagnosis. Treatment of individuals with these rare conditions is guided largely by clinical and biochemical features, with current 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 recently 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, given their infrequency, and the interindividual variability in their aetiology and phenotypic expression. This EAS Task Force consensus statement addresses these concerns by providing accessible clinical guidance for clinicians, aiming to improve diagnosis and initiation of appropriate treatment options.

The Task Force recognises, however, several unmet needs in this setting. These include practical difficulties, relating to technologies and the cost of and access to current diagnostic modalities and emerging therapies. Key deterrents are the lack of information about these disorders, specifically with respect to prevalence, pathophysiology, and outcomes, as well as the lack of effective treatments for certain 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 when the entire global population of individuals with a rare dyslipidaemia may number in the few hundreds or thousands. A potential geopolitical issue is ensuring access to diagnosis and management of these largely autosomal recessive conditions in regions with high rates 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, in terms of improvement in awareness, management, and access to effective therapy. The pharmaceutical industry may play a key role in the future, working with governments and nongovernmental organizations. Together, complementary and coordinated political, economic, socioeconomic actions together with technological advances may mitigate underdiagnosis and undertreatment, and ultimately transform health policy for the care of patients with rare lipoprotein disorders.

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Author contributions

This Task Force of the EAS was co-chaired by AL Catapano (ALC) and HN Ginsberg (HNG). The individual sections were drafted by three writing groups, focused on LDL-C (ALC, M Averna [MA], J Boren [JB], M Cuchel [MC], F Kronenberg [FK], K Parhofer [KP], FJ Raal [FJR], KK Ray [KKR], JK Stock [JKS], L Tokgözoglu [LT]); TG (HNG, RA Hegele [RAH], M Arca, D Gaudet [DG], E Stroes [ES]), and HDL (CJ Binder [CJB], LC Calabresi [LC], A von Eckardstein [AVE], RFrikke-Schmidt [RFS], GKHovingh [GKH], DLütjohann [DL], ARemaley [AR]). The draft was reviewed by the Co-Chairs, JB, MJ Chapman and RAH. All authors reviewed and approved the final manuscript before submission.

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Websites for health professionals, patients and families:

National Organization for Rare Diseases; https://rarediseases.org/
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/
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Apolipoprotein (apo) B-containing lipoproteins are produced by the intestine (A) and liver (B). Tissue-specific editing of APOB RNA produces either shorter apo B-48 or full-length apo B-100 to serve as the scaffold of particle assembly in the intestine or liver, respectively. Exogenous dietary fatty acids and sterols are actively absorbed; plant sterols are immediately re-secreted into the intestinal lumen by ATP-binding cassette protein 5 and 8 (ABCG5/8) half-transporters. Exogenous and endogenous (i.e. newly synthesised) lipids within, respectively, enterocytes and hepatocytes, are packaged into lipoprotein precursors by microsomal triglyceride-transfer protein (MTP), which catalyses co-translational transfer of triglyceride (TG) to nascent B-48 or B-100 during assembly of chylomicrons or very-low density lipoprotein (VLDL) particles in enterocytes or hepatocytes, respectively. Chylomicron formation also requires Sar1 homolog B GTPase encoded by SAR1B. After traversing the intestinal lymphatics, chylomicrons enter the circulation, where the TG content is hydrolysed by lipoprotein lipase (LPL) resulting in delivery of fatty acids to local tissues. Lipase maturation factor 1 (LMF1) is an intracellular chaperone required for LPL secretion, while glycosylphosphatidylinositol-anchored high density lipoprotein-binding protein 1 (GPIHBP1) stabilises LPL at the endothelial surface. Apolipoprotein (apo) C-II (APOC2) and A-V (APOA5) promote, while apo C-III (APOC3) and angiopoietin like protein 3 (ANGPTL3) inhibit LPL activity. The remodeled smaller lipoprotein remnants are cleared by receptor mediated mechanisms involving apo E.

Circulating TG-rich VLDL similarly undergoes LPL-mediated hydrolysis (with similar relationships to interacting molecules, not shown) forming smaller intermediate density lipoprotein (IDL), which is further processed by hepatic lipase (HL) to yield cholesterol-rich low-density lipoprotein (LDL), which in turn delivers cholesterol to peripheral cells. Some LDLS are ultimately catabolised by the hepatic LDL receptor (LDLR). Since it uniquely contains the receptor-binding domain, B-100 is the responsible ligand for the LDL receptor. The LDL-LDL receptor complex is internalised and transits though a well characterised pathway that requires the LDL receptor-associated protein (LDLRAP1). LDL contents are degraded in lysosomes by lysosomal acid lipase (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 proprotein convertase subtilisin kexin type 9 (PCSK9). LDL lipids within lysosomes are degraded by lysosomal acid lipase (LIPA).

Reverse cholesterol transport is shown in C. Apo A-I (A-I) produced by the liver and intestine constitutes the primary protein of HDL particles. ATP-binding cassette transporter A1 (ABCA1) is ubiquitously expressed and effluxes phosphatidylcholines and unesterified cholesterol from the plasma membrane to lipid-poor apo A-I or prebeta1-HDL (pβ1) and small HDL particles. pβ1-HDL is transformed to a small, discoidal particle that is the target of lecithin-cholesterol acyltransferase (LCAT), which is activated by apo A-I, uses phosphatidylcholine and unesterified cholesterol as substrates, and generates cholesteryl esters. The LCAT derived cholesteryl esters are transferred by cholesteryl ester transfer protein (CETP) to VLDL/LDL or directly delivered to the liver via scavenger receptor (SR-BI).

**Figure 1.** Lipid metabolism focusing on causal factors in rare dyslipidaemias.
Figure 2. Clinical findings in selected rare dyslipidaemias

↑ Low density lipoprotein cholesterol (LDL-C) disorders: familial hypercholesterolaemia (FH).
A: xanthelasmas; B: arcus cornealis in a five year-old girl with homozygous FH; C: extensor tendon xanthomas (arrows); D: Achilles tendon xanthomatosis (arrow); E: raised planar xanthomas in homozygous FH; F: elbow tubero-eruptive xanthomas in homozygous FH; G: severe tuberous xanthomatosis of the hands in autosomal recessive hypercholesterolaemia; H: post mortem dissected aortic valve region from a five year-old girl with sitosterolaemia showing severe atherosclerosis within the white line and occluded coronary artery ostia indicated by arrows.

↓ LDL-C 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 on microscopy with triglyceride staining red (as seen in abetalipoproteinaemia, homozygous hypobetalipoproteinaemia or chylomicron retention disease).

↑ Triglyceride (TG) disorders: monogenic chylomicronaemia.
L: Lipemic plasma on left (normal plasma on right); M: eruptive xanthomas on abdomen; N: lipaemia retinalis on fundoscopy.

↓ High density lipoprotein cholesterol (HDL-C disorders.
O, P, Q: planar xanthomas in patients with apolipoprotein (apo) A-I deficiency; R, S, T: Enlarged tonsils of patients with Tangier disease; U, V, W: Age-dependent progression of corneal opacities in patients with lecithin-cholesterol acyltransferase (LCAT) deficiency. Similar opacities are seen in patients with apo A-I deficiency who are homozygous or hemizygous for structural apo A-I variants.
**Figure 3.** Algorithm for the diagnosis and management of lipoprotein disorders characterised by very high LDL-C levels.

Abbreviations: ABCG5 and ABCG8, genes encoding the ATP-binding cassette sub-family G members 5 and 8; ANGPTL3, angiopoietin like protein 3; APOB, gene encoding apolipoprotein B; LDL-C low-density lipoprotein cholesterol; 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 Rx, therapy

**Figure 4.** Algorithm for the diagnosis and management of lipoprotein disorders characterised by very low or undetectable LDL-C levels.

Abbreviations: ABL, abetalipoproteinemia; ANGPTL3 gene encoding angiopoietin-like 3; APOB gene encoding apolipoprotein B; CRD, chylomicron retention disease; FCH, familial combined hypolipidaemia; FHBL, familial hypobetalipoproteinemia; LDL-C low-density lipoprotein cholesterol; MTTP gene encoding microsomal triglyceride transfer protein; NGS, next generation sequencing; PCSK9 gene encoding the enzyme proprotein convertase subtilisin/kexin type 9; SAR1B gene encoding GTP-binding protein SAR1b; TG triglycerides

**Figure 5.** Algorithm for the diagnosis of severe hypertriglyceridaemia.

Abbreviations: APOA5, gene encoding apolipoprotein (apo) A-V; APOC2, gene encoding apo C-II; abetalipoproteinemia; GPIHBP1, gene encoding glycosylphosphatidylinositol-anchored HDL-binding protein 1; LMF1, gene encoding lipase maturation factor 1; NGS, next generation sequencing; TG triglycerides

**Figure 6.** Algorithm for the diagnosis and management of low HDL cholesterol (hypoalphalipoproteinemia)

Abbreviations: ABCA1, gene encoding ATP-binding cassette protein type A1; APOA1, gene encoding apolipoprotein A1; ASCVD, atherosclerotic cardiovascular disease; HDL-C, high density lipoprotein cholesterol; LCAT, gene encoding lecithin cholesterol acyl transferase; NGS, next generation sequencing
# Table 1. Definition of ‘rare’ disease: Europe versus USA

<table>
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<tr>
<th>Region/Agency</th>
<th>Definition</th>
<th>Cases/100,000 of the general population</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Union/ European Medicines Agency(^2)</td>
<td>Life-threatening or chronically debilitating conditions that affect no more than 5 in 10,000 people in the EU.</td>
<td>50</td>
</tr>
<tr>
<td>USA/ Food and Drug Administration(^3)</td>
<td>Any disease or condition that (1) affects &lt;200,000 persons in the USA, OR 2) affects &gt;200,000 in the USA and for which there is no reasonable expectation that the cost of developing and making available in the USA a drug for such disease or condition will be recovered from sales in the USA of such a drug</td>
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### Table 2. Monogenic lipoprotein disorders

<table>
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<th>Phenotype</th>
<th>Disorder</th>
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<th>Gene</th>
<th>Chr</th>
<th>MIM reference number(s)</th>
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<td>↑ LDL-C (Hyperbetalipoproteinemia)</td>
<td>Familial hypercholesterolaemia</td>
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<td>LDLR</td>
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<td>Familial defective apo B-100</td>
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<td>Autosomal dominant hypercholesterolaemia type 3</td>
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<td>PCSK9</td>
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<td>Autosomal recessive hypercholesterolaemia</td>
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<td>LDLRAP1</td>
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<td>Lysosomal acid lipase deficiency</td>
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<td>↓ LDL-C (Hypobetalipoproteinemia)</td>
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<td>MTTP</td>
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<td>Homozygous hypobetalipoproteinemia</td>
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<td>Chylomicron retention disease (Anderson disease)</td>
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<td>Familial combined hypolipidaemia</td>
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<td>Hypobetalipoproteinemia, PCSK9 deficiency</td>
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<td>↑ TG</td>
<td>Monogenic chylomicronemia (formerly type 1 HLP)</td>
<td>AR</td>
<td>LPL</td>
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<td>APOC2</td>
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<td>- Apo C-II deficiency</td>
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<td>- Apo A-V deficiency</td>
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<td>- Lipase maturation factor 1 deficiency</td>
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<td>GPIHBP1</td>
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<td>- GPIHBP1 deficiency</td>
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<td>GPIHBP1</td>
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<td>Infantile hypertriglyceridaemia, transient</td>
<td>AR</td>
<td>GPD1</td>
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<td>Dysbetalipoproteinemia (formerly type III HLP)</td>
<td>Complex</td>
<td>APOE</td>
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<td>↓ HDL-C (Hypoalphalipoproteinemia)</td>
<td>Tangier disease</td>
<td>ACD*</td>
<td>ABCA1</td>
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<td>205400, 600046</td>
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<td>Apo A-I deficiency</td>
<td>ACD*</td>
<td>APOA1</td>
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<td>LCAT deficiency; Fish eye disease</td>
<td>ACD*</td>
<td>LCAT</td>
<td>16q22</td>
<td>245900, 136120, 606967</td>
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<tr>
<td>↑ HDL-C (Hyperalphalipoproteinemia)</td>
<td>Cholesteryl ester transfer protein deficiency</td>
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<td>Scavenger receptor 1 deficiency</td>
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<td>SCARB1</td>
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<td>Hepatic lipase deficiency</td>
<td>ACD</td>
<td>LIPC</td>
<td>15q21</td>
<td>614025, 151670</td>
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</tbody>
</table>

**Abbreviations:** 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 phenotype about half as extreme as homozygotes); AD, autosomal dominant; apo, apolipoprotein; ANGPTL3, gene encoding angiopoietin like protein 3; APOA1, gene encoding apolipoprotein A1; APOA5, gene encoding apolipoprotein (apo) A-V; APOB, gene encoding apolipoprotein B; APOC2, gene encoding apo C-II; APOE, gene encoding apolipoprotein E; AR, autosomal recessive; Chr, chromosomal location; CETP, gene encoding cholesterol ester transfer protein; GPD1, gene encoding glycerol-3-phosphate dehydrogenase 1; GPIHBP1, glycosylphosphatidylinositol-anchored high density lipoprotein-binding protein 1; LDL-C, low density lipoprotein cholesterol; LPL, lipoprotein lipase; LCAT, gene encoding lecithin cholesterol acyl transferase; LDL-C low-density lipoprotein cholesterol; 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, 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; NGS, next generation sequencing; PCSK9 gene encoding the enzyme proprotein convertase subtilisin/kexin type 9; SAR1B gene encoding GTP-binding protein SAR1b; SCAR1B gene encoding scavenger receptor 1B; TG, triglycerides
Table 3. Secondary causes of low HDL cholesterol

<table>
<thead>
<tr>
<th></th>
<th>Very low HDL cholesterol (&lt;0.5 mmol/L)</th>
<th>Moderately low HDL cholesterol (&lt; normal laboratory range)</th>
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</thead>
<tbody>
<tr>
<td><strong>Underlying diseases</strong></td>
<td>• Severe hypertriglyceridaemia</td>
<td>• Moderate hypertriglyceridaemia</td>
</tr>
<tr>
<td></td>
<td>• Uncontrolled diabetes</td>
<td>• Type 2 diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>• Liver failure (acute hepatic failure, congested liver/right heart failure, primary biliary liver cirrhosis)</td>
<td>• Obesity</td>
</tr>
<tr>
<td></td>
<td>• Systemic / acute inflammation</td>
<td>• Chronic inflammation</td>
</tr>
<tr>
<td></td>
<td>• Haemato-oncological diseases (acute lymphoblastic leukaemia, chronic myelogenous leukaemia, multiple myeloma)</td>
<td>• Growth hormone excess</td>
</tr>
<tr>
<td><strong>Life style, drugs</strong></td>
<td>• Androgens (testosterone, anabolic drugs)</td>
<td>• Hypercortisolism</td>
</tr>
<tr>
<td></td>
<td>• Probucol</td>
<td>• Chronic kidney disease</td>
</tr>
<tr>
<td></td>
<td>• Smoking</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Physical inactivity</td>
<td>• Some beta-blockers</td>
</tr>
<tr>
<td></td>
<td>• Thiazide-diuretics</td>
<td>• Anti-retroviral drugs</td>
</tr>
<tr>
<td></td>
<td>• Some beta-blockers</td>
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</tbody>
</table>
**Table 4. Novel therapeutics for selected rare lipid disorders**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Name</th>
<th>Mechanism of action</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>HoFH</td>
<td>lomitapide</td>
<td>Oral MTP inhibitor</td>
<td>approved in North America, Europe, Latin America and Asia</td>
</tr>
<tr>
<td>HoFH</td>
<td>mipomersen</td>
<td>Anti-APOB antisense</td>
<td>approved in US, Japan</td>
</tr>
<tr>
<td>HoFH</td>
<td>AAV8.TBG.hLDLR (RGX-501)</td>
<td>LDLR gene therapy</td>
<td>phase 1</td>
</tr>
<tr>
<td>HoFH; monogenic chylomicronemia</td>
<td>evinacumab</td>
<td>Anti-ANGPTL3 antibody</td>
<td>phase 2-3</td>
</tr>
<tr>
<td>monogenic chylomicronemia</td>
<td>alipogene tiparovec</td>
<td>LPL gene therapy</td>
<td>development suspended</td>
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<tr>
<td>monogenic chylomicronemia</td>
<td>volanesorsen</td>
<td>Anti-APOC3 ASO</td>
<td>approved in Europe</td>
</tr>
<tr>
<td>Low HDL-C</td>
<td>CSL-112/CER-001</td>
<td>Synthetic HDL infusion</td>
<td>phase 3</td>
</tr>
<tr>
<td>LCAT deficiency</td>
<td>ACP-501</td>
<td>Recombinant LCAT</td>
<td>phase 1</td>
</tr>
<tr>
<td>LAL deficiency</td>
<td>sebelipase alfa</td>
<td>LAL replacement</td>
<td>approved in North America, Europe, Latin America and Asia</td>
</tr>
</tbody>
</table>

**Abbreviations:** ANGPTL3, angiopoietin like protein 3; APOA1, apolipoprotein A-I; APOB, apolipoprotein B; APOC3, apolipoprotein C-III; HDL, high density lipoprotein; HoFH, homozygous familial hypercholesterolaemia; HDL-C, high-density lipoprotein cholesterol (HDL-C); LAL, lysosomal acid lipase; LCAT, lecithin cholesterol acyl transferase; LDLR, low density lipoprotein receptor; LPL, lipoprotein lipase; MTP, microsomal triglyceride transfer protein
Box 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
Box 2. Treatment of chylomicronaemia syndrome

**Long term diet and pharmacological intervention**
- low fat diet; recommended at <10% of calories of fat (although compliance is poor)
- avoid alcohol
- reduce intake of high glycaemic food items
- medium chain fatty acids for caloric supplementation and dietary variety
- high doses (4 g) of omega-3 fatty acids, although relatively ineffective in monogenic chylomicronaemia
- fibrates, although relatively ineffective in monogenic chylomicronaemia

**During episodes of acute pancreatitis**
- complete fasting during the first few days with parenteral fluid support and analgesia
- in patients with diabetes, intravenous insulin
- plasmapheresis or plasma exchange is generally not recommended
- management of secondary causes

**Newer or investigational treatments**
- LPL gene therapy (alipogene tiparvovec)
- anti-APOC3 antisense (volanesorsen; AKCEA-APOCIII-LRx)
- anti-ANGPTL3 therapies (evinacumab; IONIS-ANGPTL3-LRx)
Box 3. Laboratory assessment of patients with rare dyslipidaemias

**Baseline lipid evaluation**
- lipoprotein profile: total, low-density lipoprotein and high-density lipoprotein cholesterol and triglyceride
- apolipoproteins B and A-I
- Lipoprotein(a)

**Screening for secondary causes of dyslipidaemia**
- diabetes: fasting glucose, glycated hemoglobin
- hypothyroidism: thyroid stimulating hormone
- liver disease: transaminases, bilirubin, alkaline phosphatase, gamma glutamyl transferase
- renal disease: serum creatinine, urinary albumin, albumin to creatinine ratio
- autoimmune diseases: serum rheumatoid factor, antinuclear antigen, C-reactive protein

**Associated abnormalities**
- hematologic: abnormal erythrocyte morphology in low LDL-C states and LCAT deficiency
- coagulation: prolonged international normalized ratio in low LDL-C states
- serum fat soluble vitamin levels: depressed in low LDL-C states
- serum pancreatic lipase: elevated in hypertriglyceridemia-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 low LDL-C states, hepatosplenomegaly in monogenic chylomicronemia

**Diagnostic targeted sequencing panel or exome slice for dyslipidaemia genes**
- causative genes listed in Table 2

**Specialized 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-C deficiency states
Figure 1
Figure 2
LDL-C >10 mmol/L (untreated); LDL-C >8 mmol/L (treated)

Targeted NGS

Bi-allelic LDLR, APOB, PCSK9 or LDLRAP1 mutations

HoFH

- Diet, statin, ezetimibe, bile acid sequestrant
- PCSK9 inhibitor in some cases
- Selective LDL apheresis
- Newer: lomitapide, mipomersen
- Investigational: LDLR gene therapy; ANGPTL3 inhibitor (evinacumab)
- Rarely liver transplantation

Bi-allelic ABCG5/G8 mutations

Sitosterolaemia

- Low plant sterol diet
- Ezetimibe, bile acid sequestrant

Bi-allelic LIPA mutation

Atypical LALD presentation

- Diet, statin, ezetimibe
- LAL replacement therapy (sebelipase alpha)

Rule out secondary causes: nephrotic syndrome, primary biliary cirrhosis, untreated hypothyroidism, anorexia, medications

Clinical assessment: xanthomas, arcus cornealis; vascular disease

LAL replacement therapy (sebelipase alpha)

Targeted NGS

 LDL-C >10 mmol/L (untreated); LDL-C >8 mmol/L (treated)
LDL-C <1.0 mmol/L

Targeted NGS

Rule out secondary causes: lipid-lowering therapy, malnutrition, malabsorption, vegan diet, severe illness, chronic liver disease, chronic pancreatitis, cystic fibrosis, end-stage renal disease, hyperthyroidism, cachexia, medications

Clinical assessment: fat intolerance; fat soluble vitamin deficiencies; apo B level; blood film (acanthocytosis in ABL and homozygous FHBL); TG level (normal in CRD), parental lipid profile (normal in ABL, CRD)

Bi-allelic MTTP mutations

Bi-allelic APOB mutations

Bi-allelic SAR1B mutations

Bi-allelic ANGPTL3 mutations

Bi-allelic PCSK9 mutations

ABL

Homozygous FHBL

CRD

FCH

PCSK9 deficiency

- Low fat diet
- High dose oral fat soluble vitamins
- Medium chain TG
- Frequent monitoring of eyes, neurological, liver

- No specific treatment
TG >10 mmol/L (three consecutive analyses); pancreatitis history

Targeted NGS

Bi-allelic LPL, APOC2, APOA5 or GPIHBP1 or LMF1 mutations

Monogenic chylomicronaemia

See Box 2

Rule out secondary causes: high-fat foods, alcohol, oestrogen-containing medications, pregnancy, obesity and insulin resistance, diabetes, hypothyroidism, renal disease, steroids

Clinical assessment: abdominal pain, eruptivexanthomas; lipaemia retinalis, hepatosplenomegaly

Heterozygous LPL, APOC2, APOA5, GPIHBP1 or LMF1 mutation; or high polygenic score; or no obvious genetic cause

Polygenic or multifactorial chylomicronaemia

See Box 2 for management of acute episodes and for long term management using existing treatment
HDL-C <0.5 mmol/L

Targeted NGS

Rule out secondary causes: see Table 3

Clinical assessment: xanthomas; tonsils; splenomegaly; corneal opacities; renal involvement; peripheral neuropathy

Bi-allelic ABCA1 mutations

Tangier disease

Bi-allelic APOA1 mutations

Apo A-I deficiency

Bi-allelic LCAT mutations

LCAT deficiency

Fish eye disease

Heterozygous ABCA1, APOA1 or LCAT mutation; or high polygenic score

Nonsyndromic low HDL-C

- Manage systemic involvement, ie tonsillar enlargement, corneal clouding, renal impairment; peripheral neuropathy
- ASCVD prevention

- Manage secondary causes if present
- ASCVD prevention

Rule out secondary causes: see Table 3