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Istituto in tecnologie avanzate e modelli assistenziali in oncologia  
Istituto di ricovero e cura a carattere scientifico

# RUOLO DEL LABORATORIO NELLA DIAGNOSI DELLE PIÙ FREQUENTI DISLIPIDEMIE

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**Congresso Regionale SIBioC – Emilia Romagna 2019:  
Presente e futuro della Medicina di Laboratorio**

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# Main lipid-metabolism pathways in the body

**Statins** reduce the plasma LDL-cholesterol level by as much as 55%. These drugs inhibit HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis. The resulting reduction in cellular cholesterol content leads to compensatory upregulation of LDL receptors and increased uptake of LDL cholesterol by cells. A meta-analysis of 26 clinical trials ( $n=169,138$ ) showed that for every 1.0 mmol/l (40 mg/dl) reduction in LDL-cholesterol level with a statin, the risk of a major cardiovascular event is reduced by about one-fifth.<sup>3</sup>

**ApoB antisense oligonucleotides** reduce the levels of apoB, LDL cholesterol, and non-HDL cholesterol by 25–30%. These compounds are short, synthetic analogues of natural nucleic acids that bind to mRNA, inhibit the synthesis of apoB and, therefore, decrease the secretion of apoB-containing lipoproteins. Whether apoB antisense oligonucleotides reduce the risk of cardiovascular events has not been tested in clinical trials, but one member of this class, mipomersen, has been approved by the FDA as an orphan drug for patients with homozygous familial hypercholesterolaemia.<sup>4</sup>

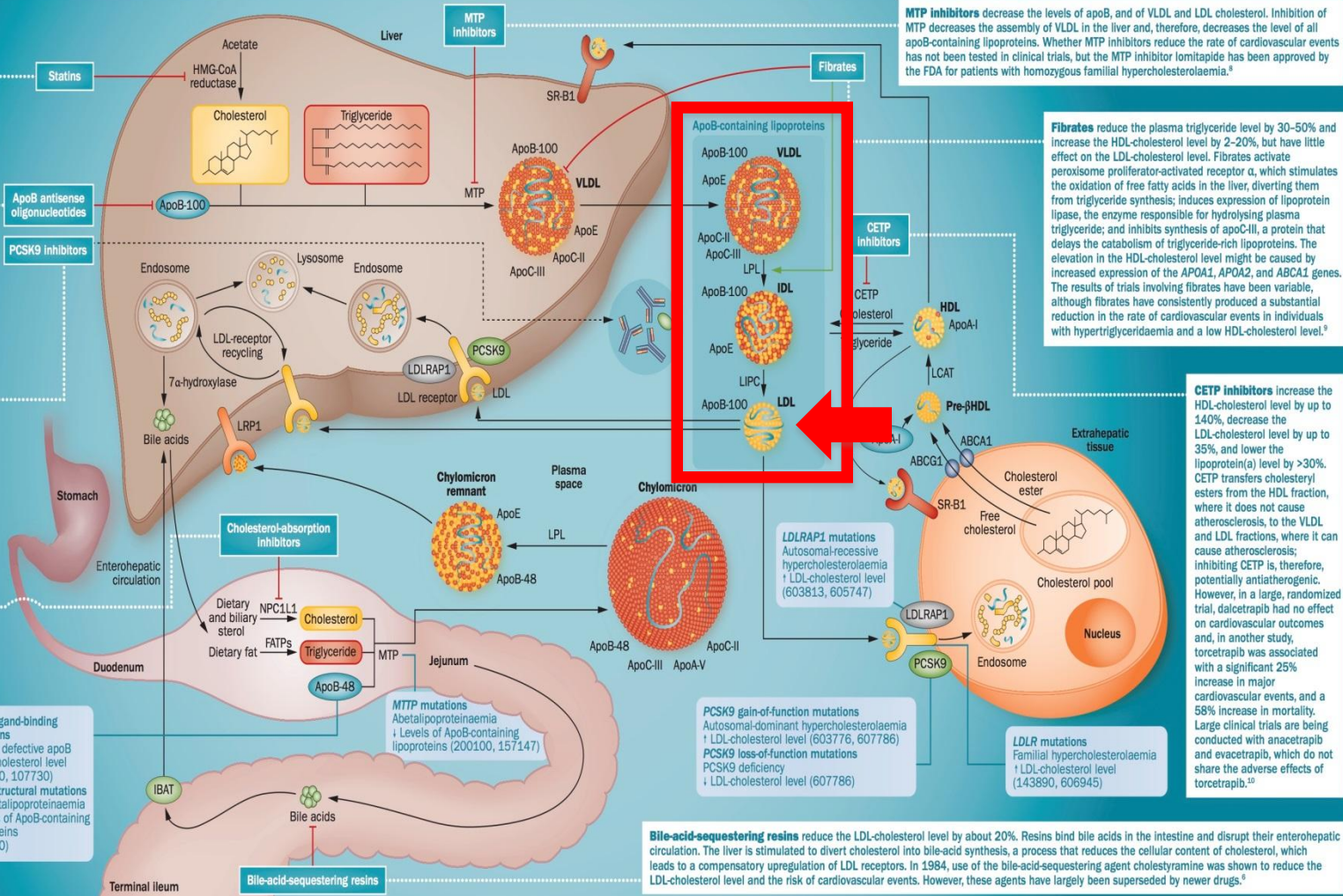
**PCSK9 inhibitors** decrease the LDL-cholesterol level by 40–70% when given either as monotherapy or in addition to a statin. PCSK9 binds to the LDL receptor and enhances its breakdown in lysosomes, reducing receptor recycling back to the surface. Therefore, inhibition of PCSK9 with, for example, monoclonal antibodies increases the expression of the LDL receptor, which results in an increased uptake of LDL cholesterol into cells, primarily hepatocytes. PCSK9 is upregulated by statins, an effect that limits the LDL-cholesterol-lowering potential of these agents, which makes PCSK9 inhibition a rational adjunctive therapy to statins. Clinical trials to test the effects of PCSK9 monoclonal antibodies on cardiovascular events are ongoing.<sup>5</sup>

**Cholesterol-absorption inhibitors**, such as ezetimibe, decrease the LDL-cholesterol level by about 18%, whether given as monotherapy or in addition to treatment with a statin. Ezetimibe reduces the absorption of cholesterol from the intestine by inhibiting NPC1L1. Reduced delivery of cholesterol to the liver increases hepatic LDL-receptor expression and, therefore, increases clearance of circulating LDL cholesterol. The use of ezetimibe to reduce the risk of cardiovascular events is being tested in the ongoing IMPROVE-IT trial.<sup>6</sup>

**Niacin** decreases the plasma levels of triglyceride, LDL cholesterol, and proatherogenic lipoprotein(a) by 30–40%, 10–15%, and up to 30%, respectively, and increases the HDL-cholesterol level by 15–30%. The mechanism of action of niacin is not certain, but involves inhibition of adipose tissue lipolysis and hepatic triglyceride synthesis. As monotherapy, niacin reduces the rate of cardiovascular events. In combination with a statin, niacin promotes regression of atherosclerosis. However, in clinical trials involving patients optimally treated with statins, niacin did not reduce the rate of cardiovascular events. The future role of niacin is uncertain.<sup>7</sup>

**APOB ligand-binding mutations**  
 Familial defective apoB  
 † LDL-cholesterol level  
 (144010, 107730)  
**APOB structural mutations**  
 Hypobetalipoproteinaemia  
 † Levels of ApoB-containing lipoproteins  
 (107730)

**IBAT**



**MTP inhibitors** decrease the levels of apoB, and of VLDL and LDL cholesterol. Inhibition of MTP decreases the assembly of VLDL in the liver and, therefore, decreases the level of all apoB-containing lipoproteins. Whether MTP inhibitors reduce the rate of cardiovascular events has not been tested in clinical trials, but the MTP inhibitor lomitapide has been approved by the FDA for patients with homozygous familial hypercholesterolaemia.<sup>8</sup>

**Fibrates** reduce the plasma triglyceride level by 30–50% and increase the HDL-cholesterol level by 2–20%, but have little effect on the LDL-cholesterol level. Fibrates activate peroxisome proliferator-activated receptor  $\alpha$ , which stimulates the oxidation of free fatty acids in the liver, diverting them from triglyceride synthesis; induces expression of lipoprotein lipase, the enzyme responsible for hydrolysing plasma triglyceride; and inhibits synthesis of apoC-III, a protein that delays the catabolism of triglyceride-rich lipoproteins. The elevation in the HDL-cholesterol level might be caused by increased expression of the APOA1, APOA2, and ABCA1 genes. The results of trials involving fibrates have been variable, although fibrates have consistently produced a substantial reduction in the rate of cardiovascular events in individuals with hypertriglyceridaemia and a low HDL-cholesterol level.<sup>9</sup>

**CETP inhibitors** increase the HDL-cholesterol level by up to 140%, decrease the LDL-cholesterol level by up to 35%, and lower the lipoprotein(a) level by >30%. CETP transfers cholesterol esters from the HDL fraction, where it does not cause atherosclerosis, to the VLDL and LDL fractions, where it can cause atherosclerosis; inhibiting CETP is, therefore, potentially antiatherogenic. However, in a large, randomized trial, dalcetrapib had no effect on cardiovascular outcomes and, in another study, torcetrapib was associated with a significant 25% increase in major cardiovascular events, and a 58% increase in mortality. Large clinical trials are being conducted with anacetrapib and evacetrapib, which do not share the adverse effects of torcetrapib.<sup>10</sup>


**Bile-acid-sequestering resins** reduce the LDL-cholesterol level by about 20%. Resins bind bile acids in the intestine and disrupt their enterohepatic circulation. The liver is stimulated to divert cholesterol into bile-acid synthesis, a process that reduces the cellular content of cholesterol, which leads to a compensatory upregulation of LDL receptors. In 1984, use of the bile-acid-sequestering agent colestyramine was shown to reduce the LDL-cholesterol level and the risk of cardiovascular events. However, these agents have largely been superseded by newer drugs.<sup>9</sup>

# **RUOLO DEL LABORATORIO NELLA DIAGNOSI DELLE PIÙ FREQUENTI DISLIPIDEMIE**

Topics:

- 1- Why do we measure Low-Density Lipoprotein (LDL) cholesterol?**
- 2- Which atherogenic lipoproteins should be measured?**
- 3- Role of Clinical Chemistry Laboratory in the diagnosis of patients with Familial Hypercholesterolemia (FH):**
  - opportunistic screening for FH using laboratory database

# 1- Why do we measure Low-Density Lipoprotein (LDL) cholesterol?

 **ESC**  
European Society  
of Cardiology

European Heart Journal (2017) **38**, 2459–2472  
doi:10.1093/eurheartj/ehx144

**CURRENT OPINION**

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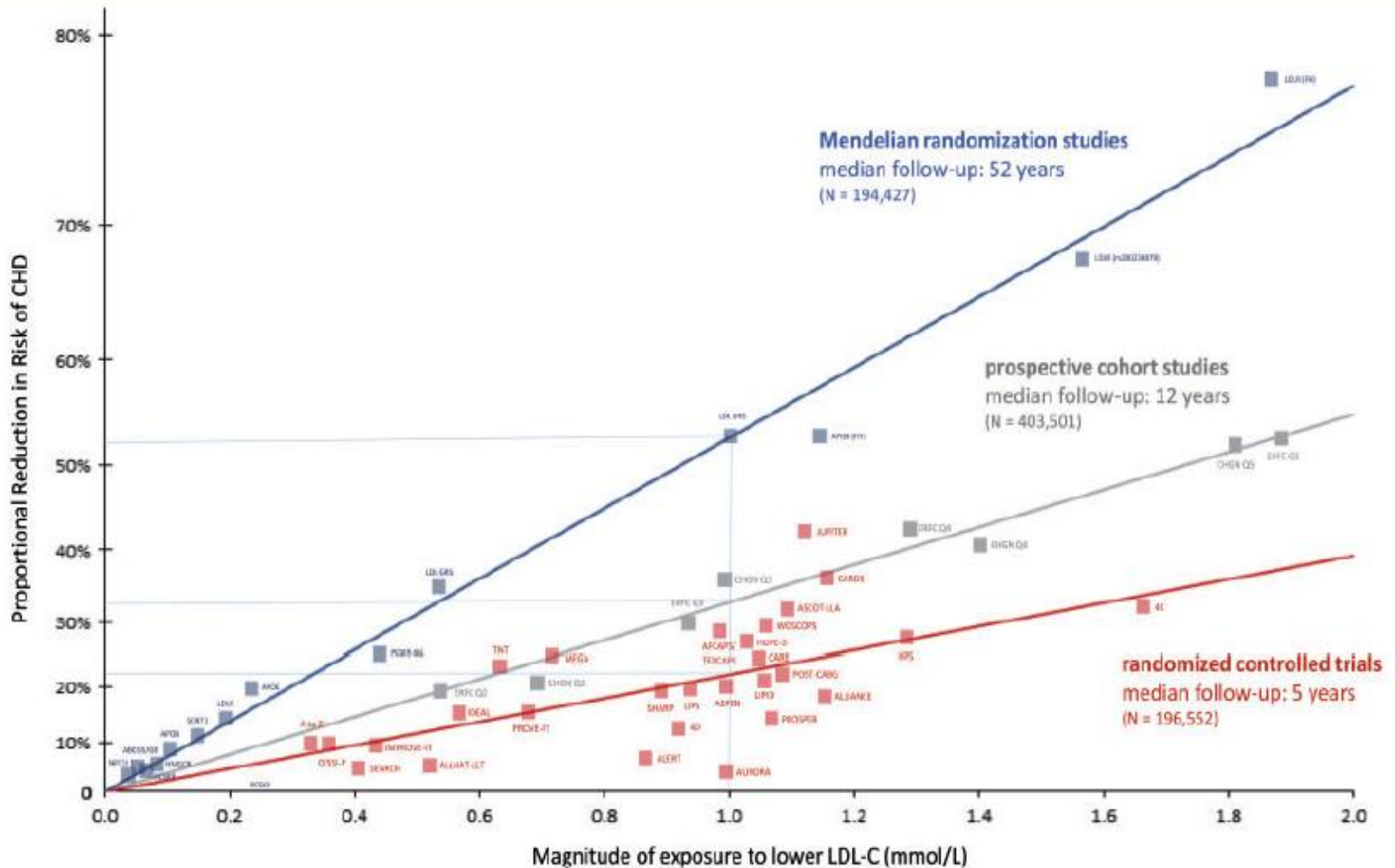
**Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel**

Brian A. Ference<sup>1\*</sup>, Henry N. Ginsberg<sup>2</sup>, Ian Graham<sup>3</sup>, Kausik K. Ray<sup>4</sup>, Chris J. Packard<sup>5</sup>, Eric Bruckert<sup>6</sup>, Robert A. Hegele<sup>7</sup>, Ronald M. Krauss<sup>8</sup>, Frederick J. Raal<sup>9</sup>, Heribert Schunkert<sup>10,11</sup>, Gerald F. Watts<sup>12</sup>, Jan Borén<sup>13</sup>, Sergio Fazio<sup>14</sup>, Jay D. Horton<sup>15,16</sup>, Luis Masana<sup>17</sup>, Stephen J. Nicholls<sup>18</sup>, Børge G. Nordestgaard<sup>19,20,21</sup>, Bart van de Sluis<sup>22</sup>, Marja-Riitta Taskinen<sup>23</sup>, Lale Tokgözoğlu<sup>24</sup>, Ulf Landmesser<sup>25,26</sup>, Ulrich Laufs<sup>27</sup>, Olov Wiklund<sup>28,29</sup>, Jane K. Stock<sup>30</sup>, M. John Chapman<sup>31†</sup>, and Alberico L. Catapano<sup>32†</sup>

- Evidence from inherited disorders of lipid metabolism
- Evidence from prospective epidemiologic studies
- Evidence from Mendelian randomization studies
- Evidence from randomized controlled trials




# Continuous, dose-dependent, and log-linear causal association between magnitude of the absolute change in LDL-C level and lifetime risk of CHD.



## 2- Which atherogenic lipoproteins should be measured?

**Clinical Chemistry** 64:7  
1006-1033 (2018)

Special Report 

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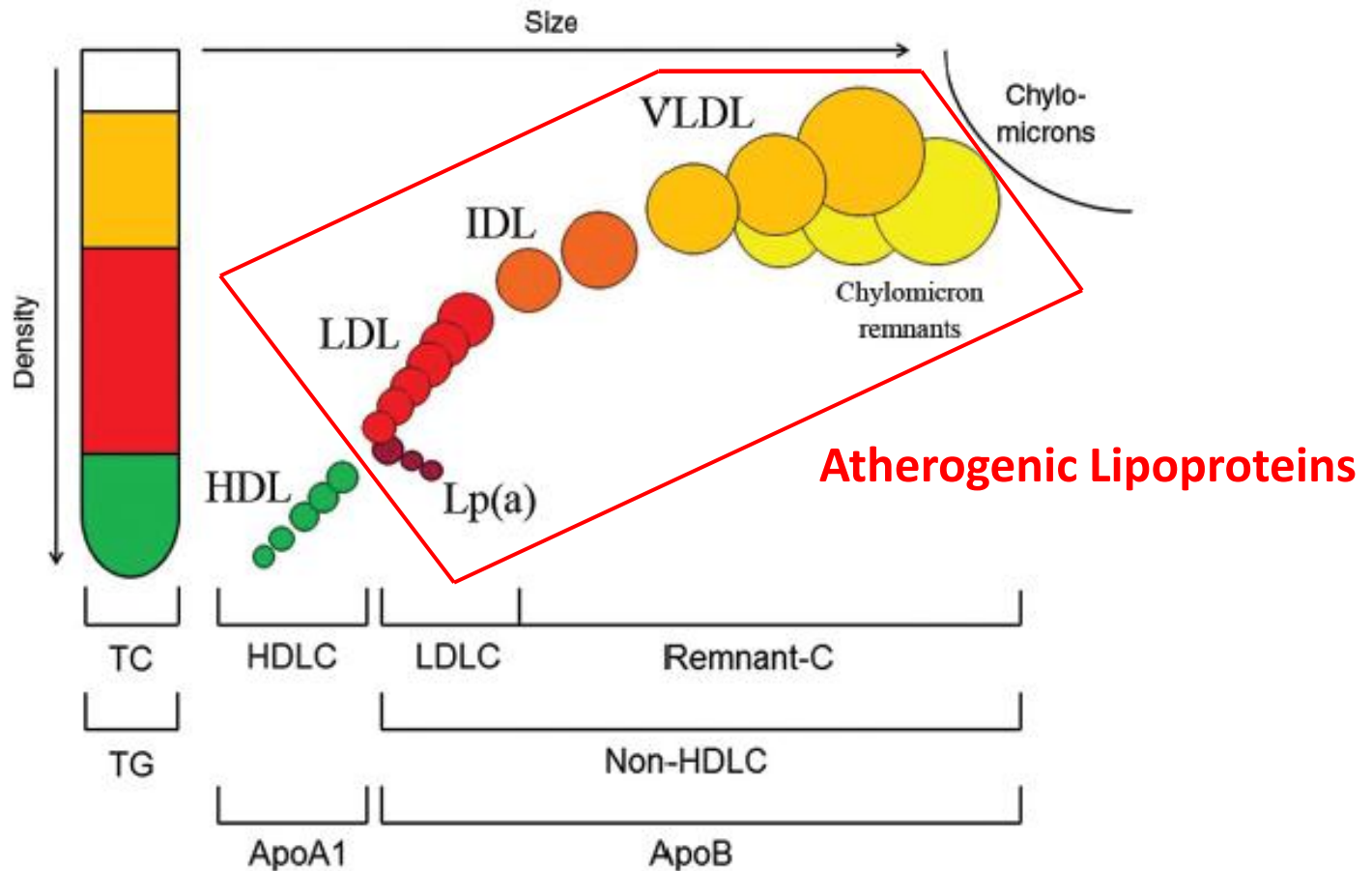
**Quantifying Atherogenic Lipoproteins:  
Current and Future Challenges in the Era of  
Personalized Medicine and Very Low  
Concentrations of LDL Cholesterol.  
A Consensus Statement from EAS and EFLM**

Michel R. Langlois,<sup>1\*</sup> M. John Chapman,<sup>2</sup> Christa Cobbaert,<sup>3</sup> Samia Mora,<sup>4</sup> Alan T. Remaley,<sup>5</sup> Emilio Ros,<sup>6</sup>  
Gerald F. Watts,<sup>7</sup> Jan Borén,<sup>8</sup> Hannsjörg Baum,<sup>9</sup> Eric Bruckert,<sup>10</sup> Alberico Catapano,<sup>11</sup>  
Olivier S. Descamps,<sup>12</sup> Arnold von Eckardstein,<sup>13</sup> Pia R. Kamstrup,<sup>14</sup> Genovefa Kolovou,<sup>15</sup>  
Florian Kronenberg,<sup>16</sup> Anne Langsted,<sup>14</sup> Kari Pulkki,<sup>17</sup> Nader Rifai,<sup>18</sup> Grazyna Sypniewska,<sup>19</sup> Olov Wiklund,<sup>8</sup>  
and Børge G. Nordestgaard,<sup>14</sup> for the European Atherosclerosis Society (EAS) and the European Federation  
of Clinical Chemistry and Laboratory Medicine (EFLM) Joint Consensus Initiative

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**European Atherosclerosis Society and  
European Federation of Clinical Chemistry and Laboratory Medicine**  
provide recommendations to optimize atherogenic lipoprotein quantification for  
cardiovascular risk management.

## 2- Which atherogenic lipoproteins should be measured?



Lipoproteins separated according to density and size and their representative laboratory markers measured in a blood sample.

## 2- Which atherogenic lipoproteins should be measured?

Table 1. Current challenges for LDLC quantification.			
Cause	Problem	Recommendation <sup>a</sup>	
<b>Analytical</b>			
Novel therapies: very low LDLC concentrations	Magnification of measurement and calculation errors (e.g., Friedewald)	CBR2, CBR3, CBR4	
Nonfasting lipid testing	Postprandial variation of TG in LDLC calculation	CBR4, CBR5	
Increasing prevalence of obesity, diabetes, and moderate or major increases in TG	Nonspecificity bias in hypertriglyceridemic (>175 mg/dL; >2 mmol/L) and dyslipidemic samples	CBR2, CBR3, CBR4, CBR9, FR1, FR2	
High Lp(a)	Overestimation of LDLC	CBR10	
<b>Clinical</b>			
Increasing prevalence of obesity and diabetes	LDLC is a less predictive marker	CBR1, CBR5, CBR6, CBR7, FR3	
Residual (on-treatment) CVD risk	Residual risk unexplained by LDLC	CBR8, FR3, FR4	
Personalized medicine	LDLC has low or no diagnostic and predictive performance in certain patients	CBR1, CBR8, FR4, FR5	

<sup>a</sup> CBR and future research recommendation (FR) to address the problem, listed in Table 2 (CBR) and Table 8 (FR).

Accumulating evidence suggests that a focus solely on the assessment and management of LDL-C is not an optimal strategy for all patients. Emerging evidence has established that VLDL, their remnants and Lp(a) likewise are causally related to CVD.



## 2- Which atherogenic lipoproteins should be measured?

**Table 3.** CBRs for the clinical indication for atherogenic lipid and lipoprotein quantification.

	CVD risk estimation	Dyslipidemia characterization	Treatment choice	Treatment target	Desirable value
TC	Yes <sup>a</sup>	Optional <sup>b</sup>	Optional <sup>b</sup>	Optional <sup>b</sup>	<190 mg/dL (5.0 mmol/L)
LDLC	Yes	Yes	Yes	Yes	Low to moderate risk <115 mg/dL (3.0 mmol/L)
					High risk <100 mg/dL (2.5 mmol/L)
					Very high risk <70 mg/dL (1.8 mmol/L)
TG	Yes	Yes	Yes	No	Fasting <150 mg/dL (1.7 mmol/L)
					Nonfasting <175 mg/dL (2.0 mmol/L)
Non-HDLC	Yes	No	No	Yes <sup>c</sup>	Moderate risk <145 mg/dL (3.8 mmol/L)
					High risk <130 mg/dL (3.3 mmol/L)
					Very high risk <100 mg/dL (2.5 mmol/L)
ApoB <sup>d</sup>	Optional <sup>c</sup>	Yes <sup>c</sup>	No	Optional <sup>c</sup>	High risk <100 mg/dL (1.0 g/L)
					Very high risk <80 mg/dL (0.8 g/L)

<sup>a</sup> In combination with HDLC.

<sup>b</sup> To be considered when LDLC is not available.

<sup>c</sup> In patients with mild to moderate hypertriglyceridemia (2-10 mmol/L; 175-880 mg/dL).

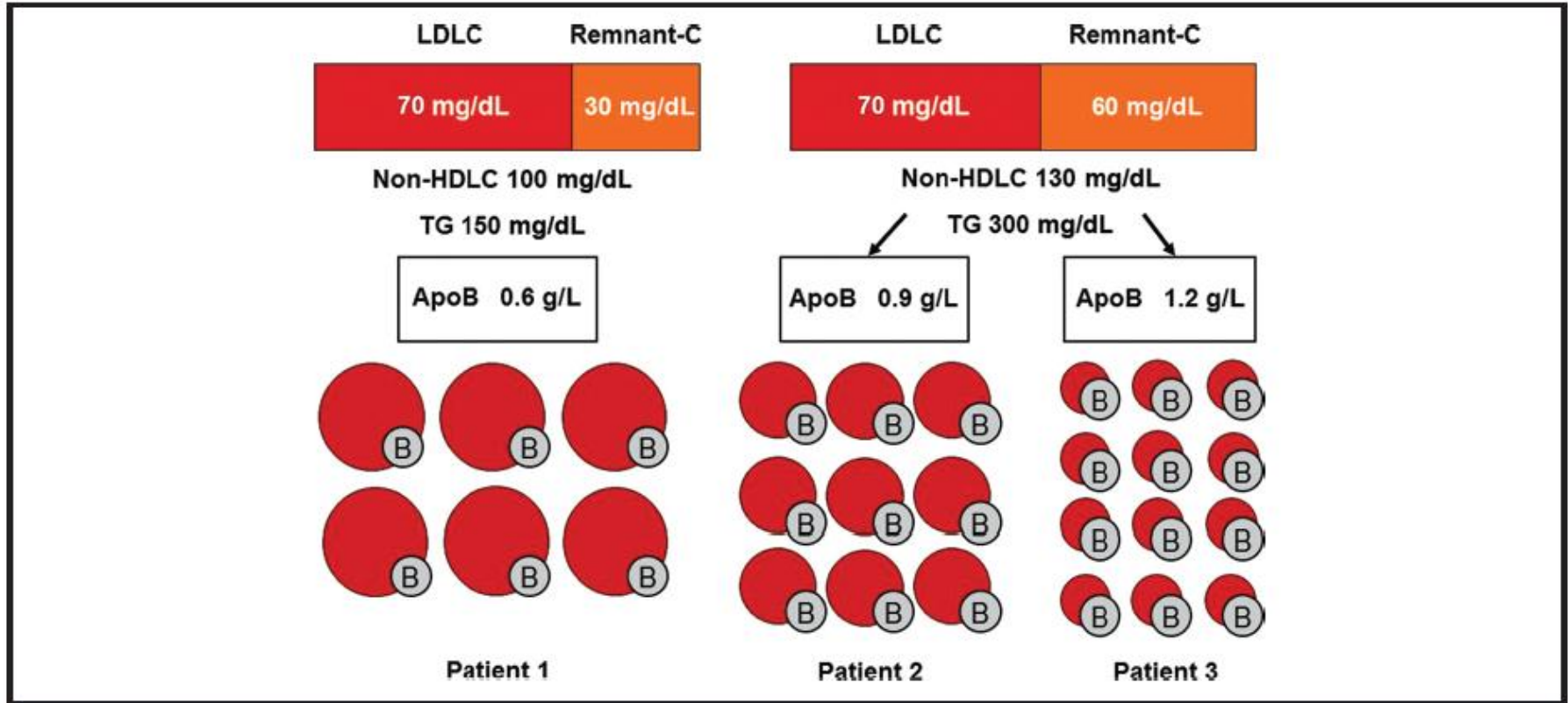
<sup>d</sup> Or LDLP if available.

To convert mmol/L to mg/dL, multiply by 38.6 for cholesterol and 88.5 for TG.

Comprehensive testing of atherogenic lipoproteins should use a biomarker, or a panel of multiple markers, that can be measured in either the fasting or nonfasting state and assesses the risk associated not only with LDL particles but also with remnant particles and Lp(a).

## 2- Which atherogenic lipoproteins should be measured?

Three patients with identical LDLC but with discordant non-HDLC and ApoB.



**Patient 1** has all 3 targets at goal and normal numbers of LDL particles (70 mg/dL).

**Patient 2** with moderate hypertriglyceridemia and discordant non-HDL-C above target (100 mg/dL).

**Patient 3** with moderate hypertriglyceridemia and increased non-HDL-C but higher ApoB concentration than patient 2 (small dense LDL particles).

## 2- Which atherogenic lipoproteins should be measured?

**Table 5.** Examples of interlaboratory uncertainty when plasma lipid parameters are determined by different methods.

Assay	Assumed total error	Defined concentration in model patient	Range of uncertainty
TC	9% <sup>a</sup>	200 mg/dL (5.2 mmol/L)	182-218 mg/dL (4.7-5.7 mmol/L)
TG	15% <sup>a</sup>	250 mg/dL (2.8 mmol/L)	212-288 mg/dL (2.4-3.3 mmol/L)
HDLc	-20% to +36% <sup>b</sup>	40 mg/dL (1.0 mmol/L)	32-54 mg/dL (0.8-1.4 mmol/L)
Non-HDLc	Derived from TC and HDLc	160 mg/dL (4.1 mmol/L)	128-186 mg/dL (3.3-4.8 mmol/L)
Measured LDLc	-26% to +32% <sup>b</sup>	110 mg/dL (2.8 mmol/L)	82-145 mg/dL (2.1-3.8 mmol/L)
Estimated LDLc (Friedewald)	Derived from TC, TG, and HDLc	110 mg/dL (2.8 mmol/L)	70-144 mg/dL (1.8-3.7 mmol/L)
ApoB	12% <sup>c</sup>	110 mg/dL (1.1 g/L)	97-123 mg/dL (0.9-1.2 g/L)

<sup>a</sup> Based on NCEP analytical performance criteria (41).

<sup>b</sup> Total error ranges observed by Miller et al. (44) across different dLDLc and dHDLc methods in dyslipidemic samples. The total error combines systematic bias and random imprecision. The tables are not relevant for the monitoring of a patient by the same laboratory/method over time. In this situation, the bias remains constant and only the (inevitable) imprecision is relevant. It will be considerably lower than the total error, at least for dHDLc and dLDLc (<10%), but not for TC, TG, and the derived measures cLDLc or non-HDLc.

<sup>c</sup> Based on AACC Lipoprotein and Vascular Diseases Division-Working Group on Best Practices assessment (38).

There are various dLDLc and dHDLc assays available based on different principles from different manufacturers to selectively isolate and measure cholesterol in these lipoproteins.

- Substantial nonselectivity errors have been reported for many of the direct assays.
  - According to National Cholesterol Education Program (NCEP) criteria, the total error of LDLc measurements should be within 12% of the true value.

## 2- Which atherogenic lipoproteins should be measured?

**Table 2.** Key CBR to improve the clinical use of atherogenic lipoprotein assays.

CBR1	Comprehensive assay(s) of atherogenic lipoproteins should assess the risk conferred by LDL particles, remnant particles, and Lp(a).
CBR2	Laboratories and clinical trial centers should report lipid profiles with declaration of the assay method/manufacture used.
CBR3	Follow-up of lipid profiles of a patient, from baseline at diagnosis to on-treatment measurements, should be ideally performed with the same assay method (and preferably the same laboratory and instrument).
CBR4	Values near the treatment decision cutpoints should be confirmed by $\geq 2$ repeated measurements by the same method and then averaged.
CBR5	Laboratories should automatically calculate and report non-HDLC on all lipid profiles.
CBR6	Non-HDLC adds Remnant-C to LDLC and can be calculated in the fasting and nonfasting state, independent of TG variability.
CBR7	ApoB assay can estimate LDLP (~95% of apoB) plus Remnant-P and Lp(a) particle numbers in the fasting and nonfasting state.
CBR8	LDLC is the primary target of lipid-lowering therapy. When LDLC goal is achieved, then non-HDLC or apoB should be preferred as secondary treatment targets in patients with TG >175 mg/dL (>2 mmol/L), obesity, metabolic syndrome, or type 2 diabetes.
CBR9	When LDLC is unavailable because of an invalid Friedewald equation (TG >400 mg/dL; 4.5 mmol/L), follow-up calculation of non-HDLC should be used at higher TG concentrations rather than additional direct LDLC measurement.
CBR10	Lp(a)-corrected LDLC should be assessed at least once in patients with suspected or known high Lp(a), or if the patient shows a poor response to LDL-lowering therapy.

# Familial Hypercholesterolemia

Estimated prevalence  
in population:  
1:250

Emilia-Romagna:  
18000 FH individuals

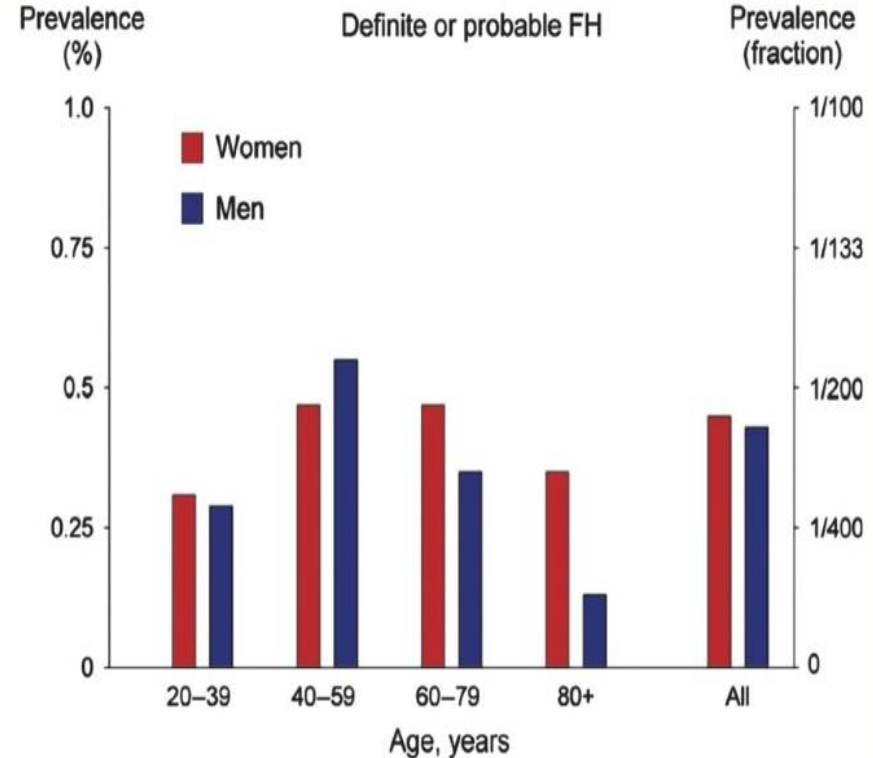
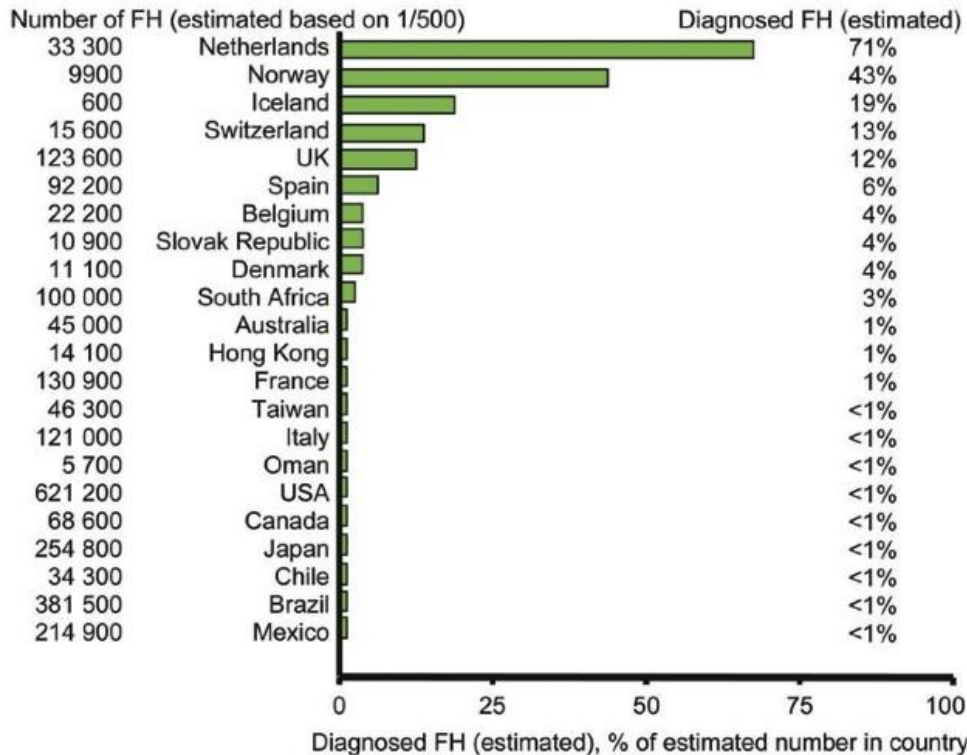


European Heart Journal (2013) 34, 3478–3490  
doi:10.1093/eurheartj/eh273

CURRENT OPINION

**Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease**

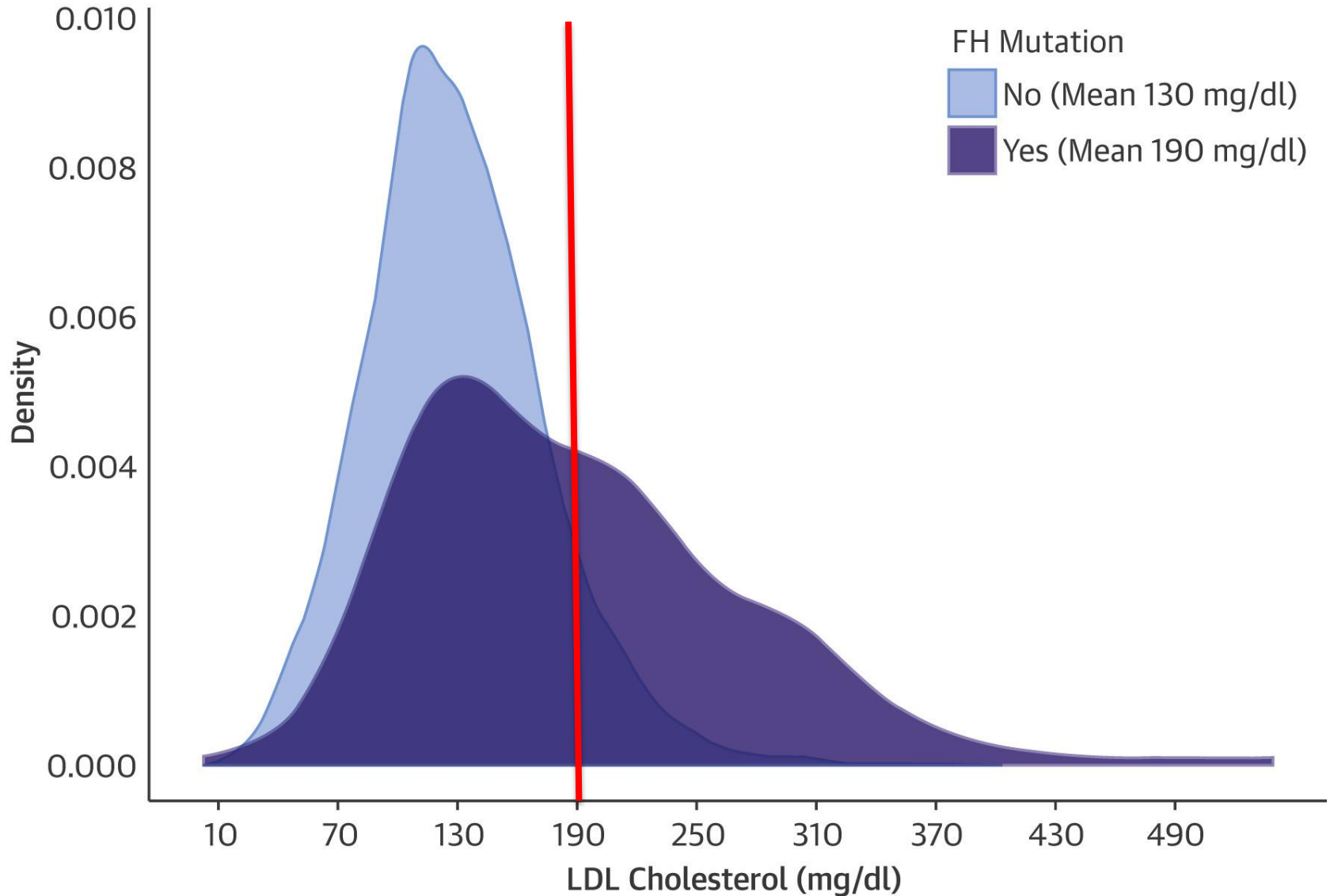
*Consensus Statement of the European Atherosclerosis Society*





### 3- Role of Clinical Chemistry Laboratory in the diagnosis of FH patients

FH is mainly characterized by a biochemical phenotype: **↑TC and ↑↑LDL**



# Clinical Scoring Systems for Familial Hypercholesterolemia

Criteria	Simon Broome Register <sup>18</sup>	Dutch Lipid Clinic Network <sup>19</sup>		MED-PED <sup>20a</sup>	AHA <sup>21</sup>	Canadian Criteria <sup>22,144</sup>
<b>Lipids</b>						
Total cholesterol (mmol/l)	<ul style="list-style-type: none"> <li>• &gt;7.5 (adult) [a]</li> <li>• &gt;6.7 (child) [a]</li> </ul>	NA		NA	NA	NA
LDL cholesterol (mmol/l)	<ul style="list-style-type: none"> <li>• &gt;4.9 (adult) [a]</li> <li>• &gt;4.0 (child) [a]</li> </ul>	<ul style="list-style-type: none"> <li>• &gt;8.5 [8]</li> <li>• 6.5–8.4 [5]</li> <li>• 5.0–6.4 [3]</li> <li>• 4.0–4.9 [1]</li> </ul>	<ul style="list-style-type: none"> <li>&gt; 330 mg/dl</li> <li>250 - 330 mg/dl</li> <li>190 - 250 mg/dl</li> <li>155 - 190 mg/dl</li> </ul>	>5.7–9.3 <sup>b</sup>	<ul style="list-style-type: none"> <li>• &gt;5.0 (adult) [a]</li> <li>• &gt;4.0 (child) [a]</li> </ul>	<ul style="list-style-type: none"> <li>• &gt;4.0 (child) [a]</li> <li>• &gt;4.5 (18–39 years) [a]</li> <li>• &gt;5.0 (&gt;40 years) [a]</li> <li>• &gt;8.5 [b]</li> </ul>
<b>Physical stigmata</b>						
Personal	Tendon xanthoma [b]	<ul style="list-style-type: none"> <li>• Tendon xanthoma [6]</li> <li>• Arcus cornealis<sup>c</sup> [4]</li> </ul>		NA	NA	Tendon xanthoma [c]
Family	Tendon xanthoma in one relative [b]	Tendon xanthoma or arcus cornealis [2]		NA	NA	NA
<b>Family history</b>						
CAD	MI aged <50 years in two relatives or aged <60 years in one relative [d]	<ul style="list-style-type: none"> <li>• Premature CAD<sup>d</sup> [2]</li> <li>• Premature CVD or PVD<sup>d</sup> [1]</li> </ul>		NA	Premature CAD in one relative [b]	Premature CAD in one relative <sup>d</sup> [d]
LDL cholesterol (mmol/l)	>7.5 in one or two relatives [e]	Child with LDL cholesterol >95th percentile [2]		NA	One affected relative [c]	One relative with high LDL-cholesterol level [d]
Genetics	NA	NA		Known FH in a relative	NA	FH mutation in one relative [c]
<b>Genetics</b>						
Genetic mutations	APOB, LDLR, or PCSK9 mutation [c]	APOB, LDLR, or PCSK9 mutation [8]		NA	APOB, LDLR, or PCSK9 mutation [d]	APOB, LDLR, or PCSK9 mutation [c]
<b>Diagnosis</b>						
Diagnosis of FH	<ul style="list-style-type: none"> <li>• Definite: a + (b or c)</li> <li>• Probable: (a + d) or (a + e)</li> </ul>	<ul style="list-style-type: none"> <li>• Definite: &gt;8</li> <li>• Probable: 6–8</li> <li>• Possible: 3–5</li> </ul>		Meets adjusted LDL-cholesterol cut-off point	a + (b or c) or d	<ul style="list-style-type: none"> <li>• Definite: (a + c) or b</li> <li>• Probable: a + d</li> </ul>

# Role of Clinical Biochemistry Laboratories

- **Clinical Biochemistry Laboratories** are ideally placed to augment the **opportunistic detection of FH**.
- Primary care physicians request the majority of lipid profiles in clinical chemistry laboratories.
- Important **role of interpretative comments** with specific recommendations to improve the **detection of FH patients**.
- **Expert computer systems** may further optimise detection of FH by incorporating information on clinical and familial history and previous laboratory results.
- Possibility to increase FH identification for inpatients through **interaction with electronic health records (EHR)**.

**Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cut-points—a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine**

# Interpretative comments on lipid profile to highlight risk of FH

**Table 8** Life-threatening and extremely abnormal concentrations with separate reporting and consequent direct referral to a lipid clinic or to a physician with special interest in lipids

	Life-threatening concentrations	Refer patient to a lipid clinic or to a physician with special interest in lipids for further assessment of the following conditions
LDL cholesterol	> 13 mmol/L > 500 mg/dL <sup>a</sup>	Homozygous familial hypercholesterolaemia with extremely high cardiovascular risk <sup>44</sup>
LDL cholesterol	> 5 mmol/L > 190 mg/dL <sup>a</sup>	Heterozygous familial hypercholesterolaemia with high cardiovascular risk <sup>43</sup>
LDL cholesterol in children	> 4 mmol/L > 155 mg/dL <sup>a</sup>	Heterozygous familial hypercholesterolaemia with high cardiovascular risk <sup>45</sup>

## Commento Interpretativo sul Profilo Lipidico:

- **LDL-C > 190 mg/dl in adulti > 18 anni:** Valore di LDL significativamente elevato. Si consiglia accurata valutazione degli eventuali fattori di rischio cardiovascolare associati.
- **LDL-C > 250 mg/dl in adulti o LDL > 190 mg/dl in soggetti < 18 anni:** I valori rilevati possono essere indicativi di una forma di Ipercolesterolemia Familiare (FH) ad elevato rischio cardiovascolare. Si consiglia una valutazione specialistica lipidologica.

**334 Referti → 68% Richiedenti Esterni → 287 Pazienti**

# Patients with FH phenotype identified through DLCN score may undergo genetic testing

Patient at risk due to family history of FH

Patient *with* FH phenotype

Cascade genetic testing

*LDLR, APOB, PCSK9* genetic testing

Positive

Negative

Genotype +  
Phenotype -

Genotype +  
Phenotype +

Genotype -  
Phenotype +

Monitor LDL-C

Treat LDL-C

Treat LDL-C and/or phenocopy condition with specific treatment recommendations

Consider alternative molecular etiologies:

- Polygenic
- High Lp(a)
- *APOE*
- As yet undiscovered FH genes
- Autosomal recessive FH (biallelic *LDLRAP1* pathogenic variants)
- Phenocopies
  - Sitosterolemia (autosomal recessive pathogenic variants in *ABCG5* or *ABCG8*)
  - Lysosomal acid lipase deficiency (autosomal recessive pathogenic variants in *LIPA*)



A blurred industrial machine, possibly a conveyor belt or assembly line, with a prominent red light source on the left. A white label with a barcode is visible on the right side of the machine. The background shows a complex industrial environment with various pipes and structures.

**GRAZIE PER L'ATTENZIONE!**