

Familial Hypercholesterolemia

Single-gene disruption of LDL clearance

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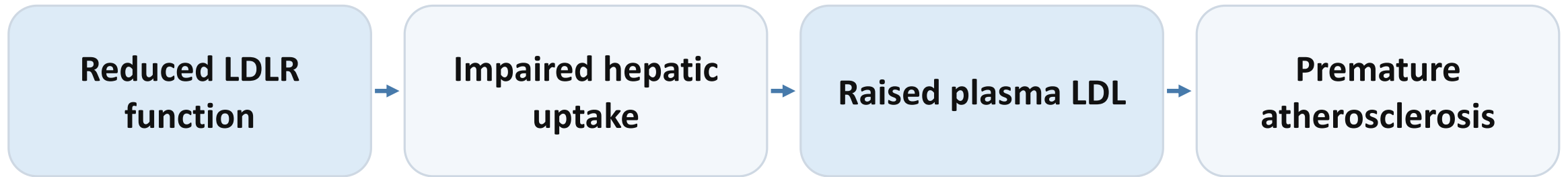
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Learning objectives

- Explain how LDL is produced and cleared by the liver.
- Distinguish LDLR, APOB and PCSK9 mechanisms of FH.
- Relate LDL receptor defects to xanthomas and premature atherosclerosis.
- Classify six functional LDLR mutation categories.
- Explain how statins and PCSK9 inhibition modify receptor availability.

Familial hypercholesterolemia: The central defect

The primary lesion is inadequate receptor-mediated removal of plasma LDL.



FH is a membrane-receptor trafficking disorder with systemic vascular consequences.

A receptor-transport model of Mendelian disease

Molecular change

- Altered receptor synthesis
- Altered receptor targeting
- Altered ligand binding
- Altered endocytosis/recycling

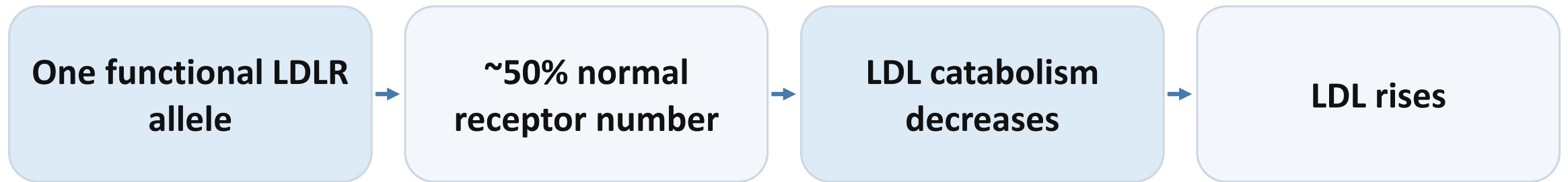
Functional effect

- Less effective hepatic LDL clearance
- Accumulation of circulating LDL
- Greater exposure of tissues to cholesterol
- Accelerated atherogenesis

The site of the molecular lesion determines the specific transport failure.

Autosomal dominant expression: One altered allele matters

Heterozygotes express disease despite retaining one working copy of LDLR.



Reduced receptor dosage is sufficient to raise LDL from birth.

Heterozygous and homozygous FH differ in severity

Feature	Heterozygous LDLR-associated FH	Homozygous LDLR-associated FH
Functional alleles	One retained	Usually none normally functioning
LDL receptors	Approximately 50% of normal	Virtually absent in severe forms
Plasma cholesterol	About 2–3× normal	About 5–6× normal
Atherosclerosis	Premature, usually adult manifestations	May appear in childhood
Myocardial infarction	Premature risk	May occur before age 20

FH is genetically heterogeneous

LDLR

Receptor protein

Most common cause

Inadequate uptake

APOB

LDL ligand ApoB-100

Reduced receptor binding

Less removal

PCSK9

Regulator of LDLR turnover

Activating variants

Faster receptor loss

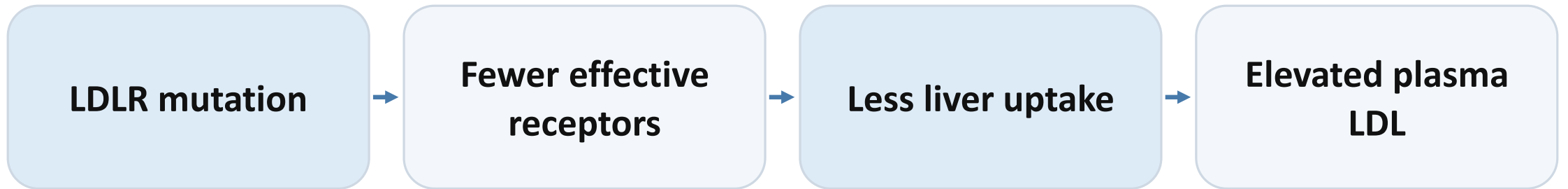
Different molecular defects converge on reduced LDLR-mediated clearance.

Genetic contributions reported

Gene	Approximate proportion of FH cases	Proximal molecular effect
LDLR	80%–85%	Receptor deficiency or dysfunction
APOB	5%–10%	Weakened LDL–LDLR binding
PCSK9	1%–2%	Excess receptor degradation

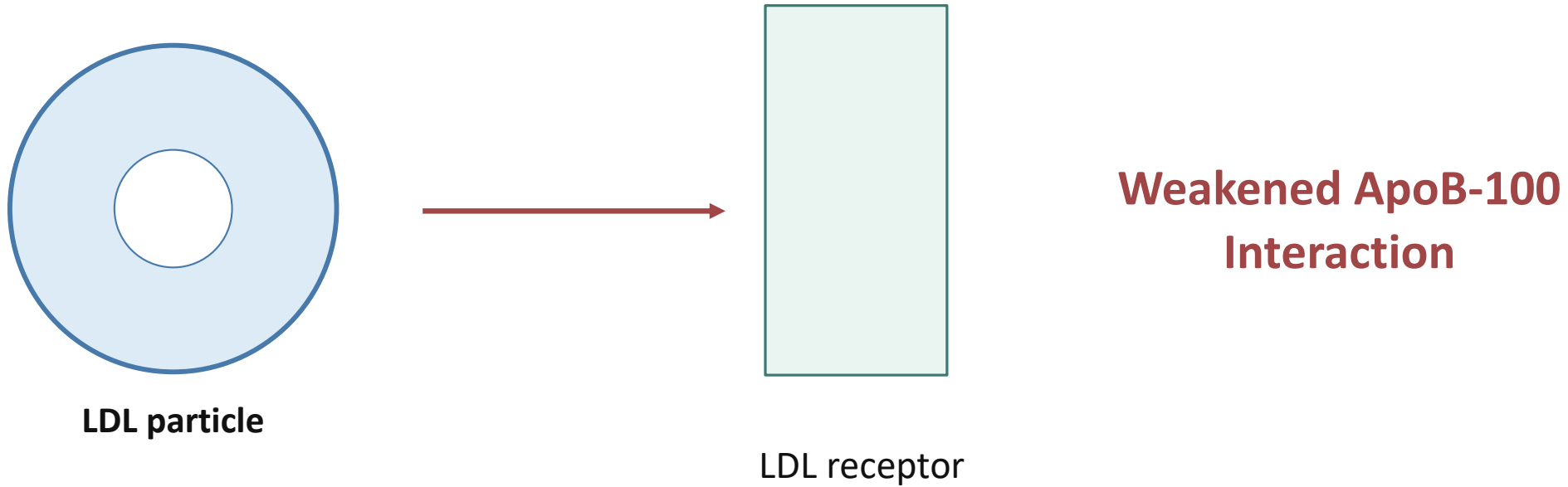
These textbook figures describe distribution, not a diagnostic test.

LDLR mutations reduce functional LDL receptors



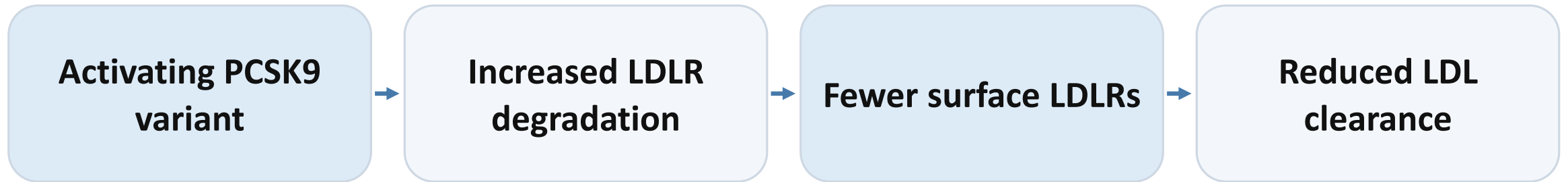
The receptor defect can alter synthesis, trafficking, binding, uptake or recycling.

APOB mutations compromise receptor recognition



A receptor can be present yet fail to efficiently capture altered LDL.

PCSK9 gain of function removes LDL receptors



PCSK9 determines how often internalized receptors are recycled versus degraded.

Three genes; One shared pathophysiologic endpoint

Lesion	Mechanistic location	Result
LDLR loss of function	The receptor itself	Reduced functional LDLR activity
APOB defective ligand	LDL particle surface	Less effective LDL attachment
PCSK9 gain of function	Receptor turnover	More LDLR lysosomal degradation

The normal body cholesterol pool has two sources

Exogenous supply

- Dietary triglycerides and cholesterol
- Intestinal incorporation into chylomicrons
- Chylomicron remnants reach liver

Endogenous supply

- Hepatic cholesterol synthesis
- Hepatic secretion of VLDL
- Conversion through IDL to LDL

FH predominantly disrupts handling of circulating LDL, not dietary absorption alone.

Dietary lipid delivery: The chylomicron route

- 1 Intestinal mucosa packages lipid as chylomicrons.
- 2 Chylomicrons enter lymphatics and then blood.
- 3 Lipoprotein lipase hydrolyzes their triglycerides in capillaries.
- 4 Cholesterol-rich remnants are delivered to the liver.

Chylomicron remnants feed the hepatic cholesterol pool.

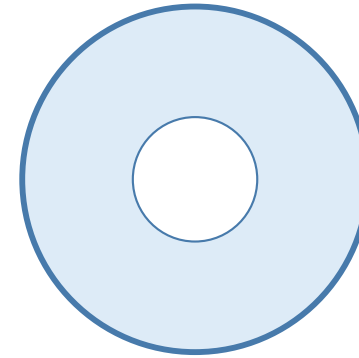
Hepatic VLDL secretion starts endogenous transport

VLDL particle

Triglyceride-rich lipoprotein

Carries ApoB, ApoC and ApoE

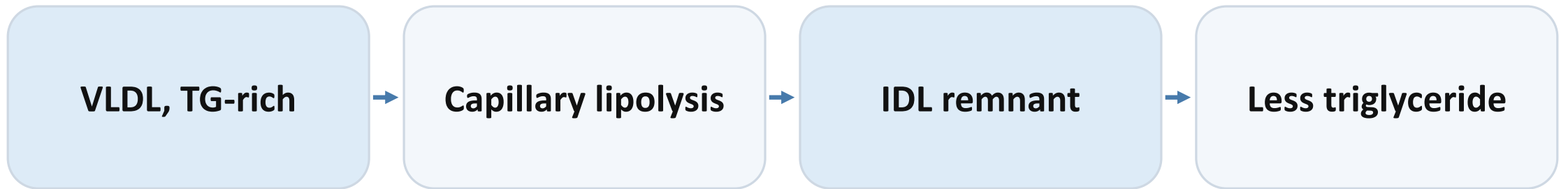
Secreted from the liver into blood



VLDL

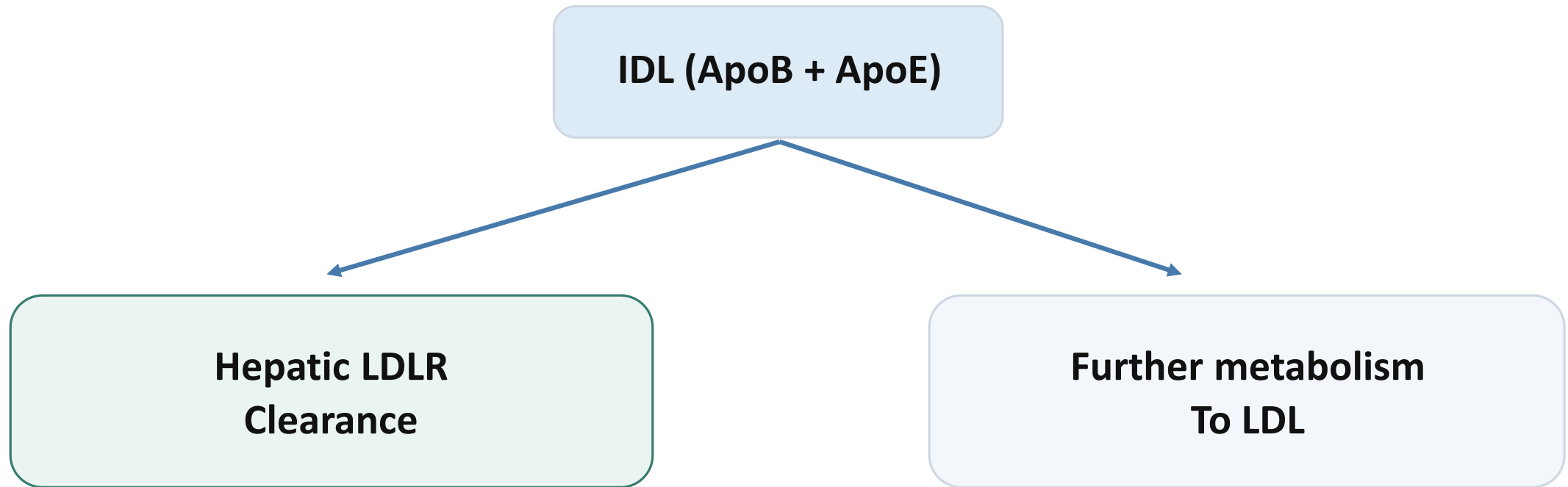
VLDL is the immediate upstream precursor of IDL.

Lipoprotein lipase converts VLDL into IDL



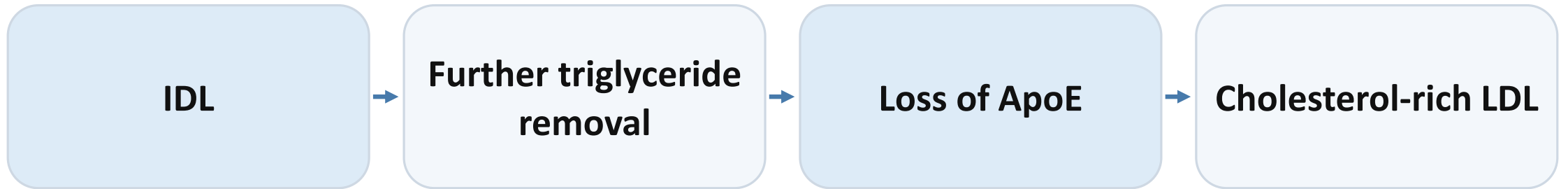
IDL retains ApoB and ApoE while ApoC is lost.

IDL has two competing metabolic fates



The liver normally clears roughly half of newly formed IDL.

LDL arises from further IDL processing



Mature LDL retains ApoB, which serves as the LDLR-recognition ligand.

ApoB and ApoE have distinct ligand roles

Lipoprotein	Relevant apolipoproteins	LDLR recognition
VLDL	ApoB, ApoC, ApoE	Precursor of IDL
IDL	ApoB and ApoE	LDLR recognizes both ligands
LDL	ApoB retained	LDLR binds via ApoB

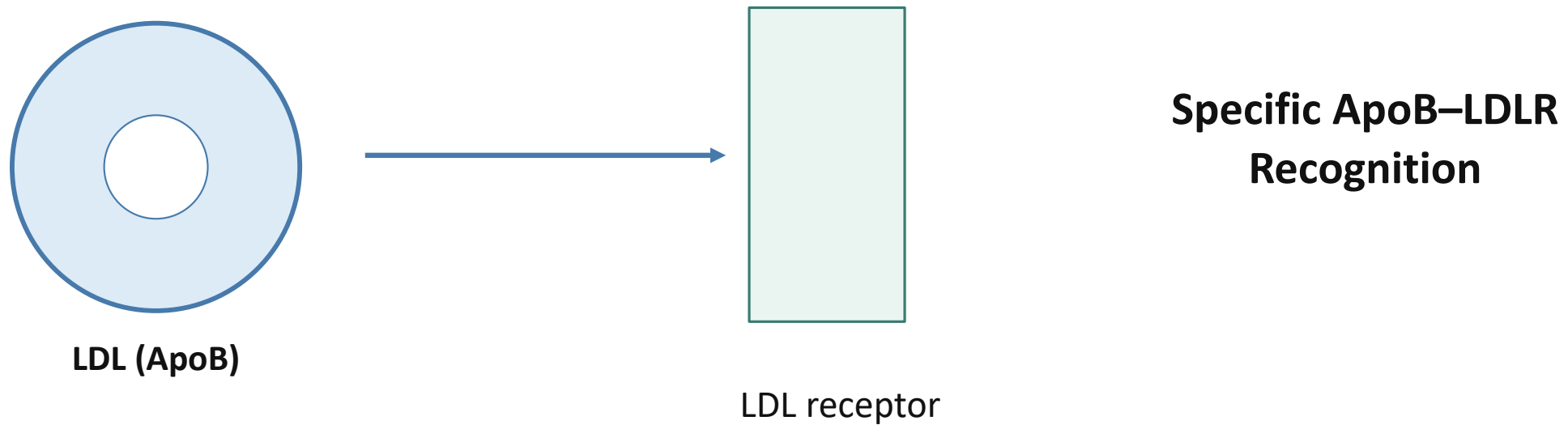
The liver is the dominant organ of LDL clearance

~70%

Of plasma LDL is normally cleared by the liver

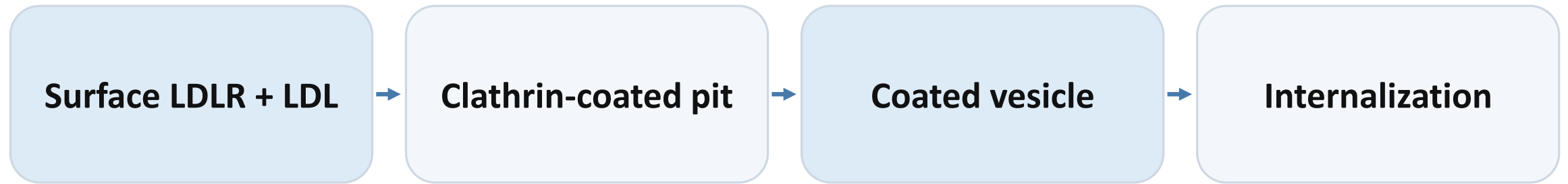
Hepatic LDLR function is therefore a major determinant of LDL residence in plasma.

LDLR-mediated uptake begins at the cell surface



Mutant ligand or receptor can disrupt this first step.

Coated pits concentrate LDL receptor complexes



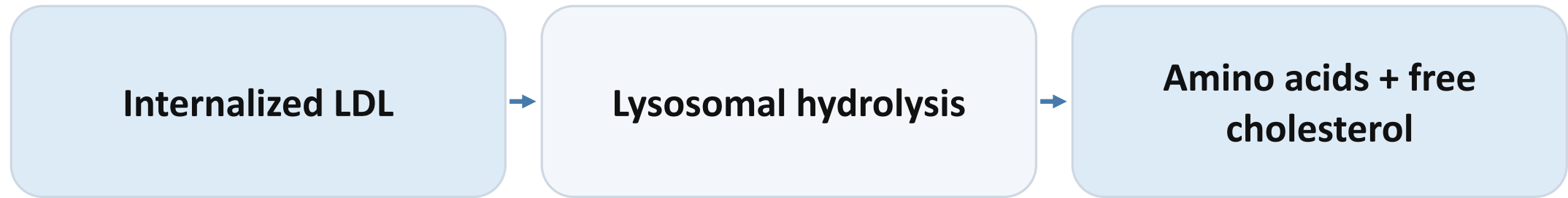
Clathrin-mediated uptake is downstream of surface binding.

Endosomal trafficking separates ligand and receptor

- 1 Receptor-bound LDL enters a coated vesicle.
- 2 The vesicle traffics into the endosomal compartment.
- 3 LDL dissociates from its receptor.
- 4 LDLR is sorted for recycling or, under PCSK9 influence, degradation.

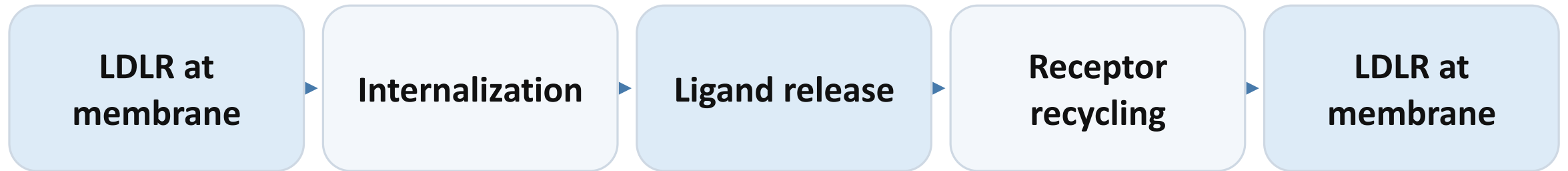
Effective recycling preserves hepatocyte surface receptor density.

Lysosomes process internalized LDL



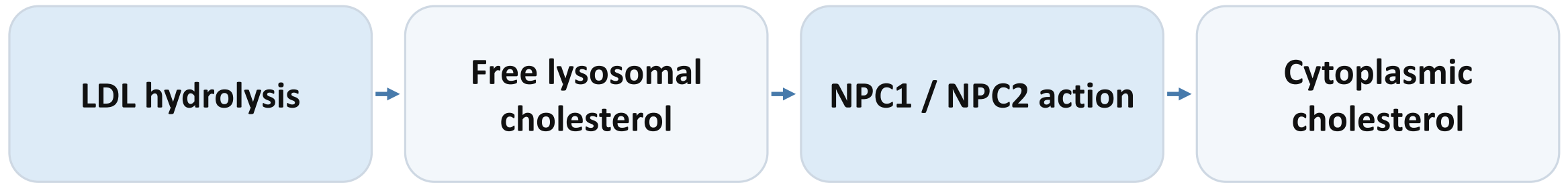
ApoB is degraded to amino acids; Cholesteryl esters yield free cholesterol.

Receptor recycling sustains repeated LDL uptake



Recycling is a distinct vulnerability from initial LDL binding.

NPC1 and NPC2 help cholesterol exit lysosomes



Intracellular cholesterol then enters biosynthesis and regulatory pathways.

Cellular cholesterol provides feedback control

Intracellular free cholesterol

- ↓ HMG-CoA reductase
- ↑ Cholesterol ester storage
- ↓ LDL receptor synthesis
- ↑ PCSK9-mediated LDLR degradation

Cholesterol inhibits de novo synthesis

More cellular cholesterol



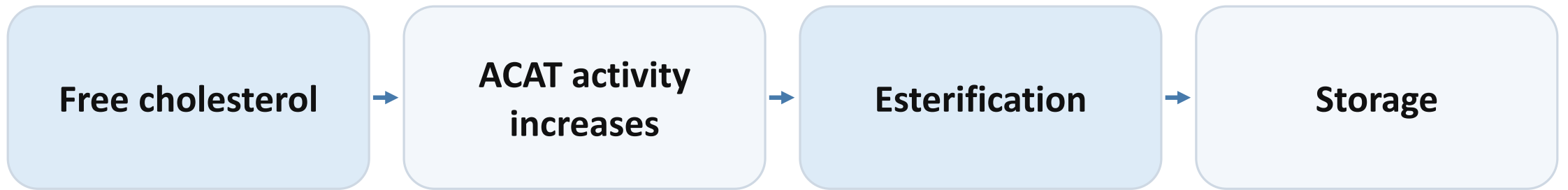
**HMG-CoA reductase
inhibited**



Less cholesterol synthesis

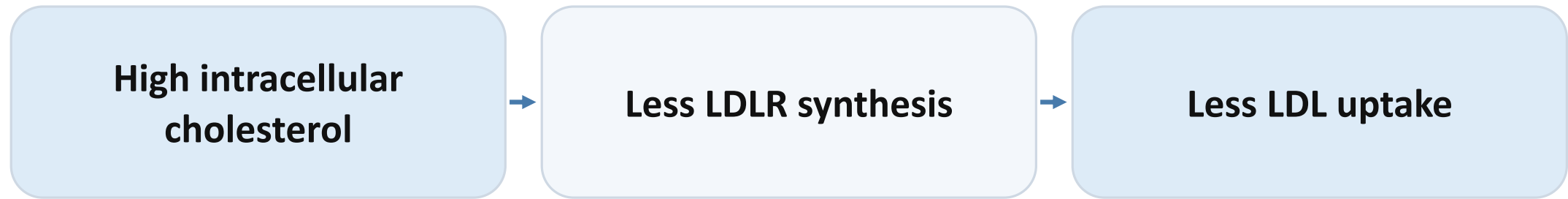
This feedback constrains endogenous synthesis when cellular cholesterol is plentiful.

Excess cholesterol can be stored as esters



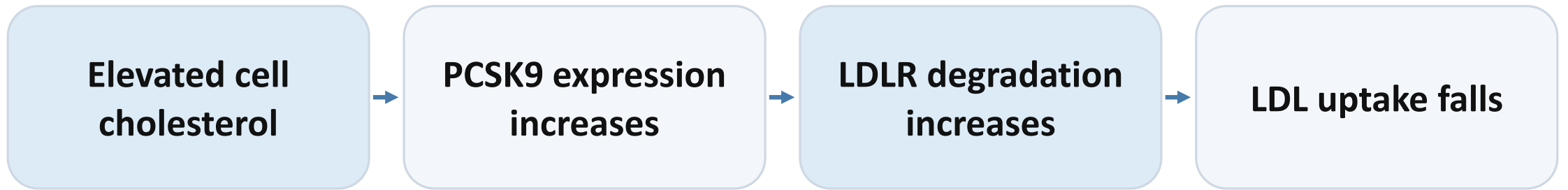
ACAT: Acyl-coenzyme A:cholesterol acyltransferase.

High cellular cholesterol suppresses LDLR synthesis



LDLR expression responds to cholesterol supply within the cell.

PCSK9 adds a receptor-degradation feedback



PCSK9 regulates receptor availability after endocytosis.

Cholesterol homeostasis integrates supply and uptake

Intracellular cholesterol

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graph TD; A[Intracellular cholesterol] --> B[Synthesis ↓]; A --> C[Ester storage ↑]; A --> D[LDLR synthesis ↓]; A --> E[Recycling ↓ via PCSK9];
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Synthesis ↓

Ester storage ↑

LDLR synthesis ↓

Recycling ↓ via PCSK9

Four responses limit further accumulation of free intracellular cholesterol.

LDLR loss impairs plasma LDL catabolism

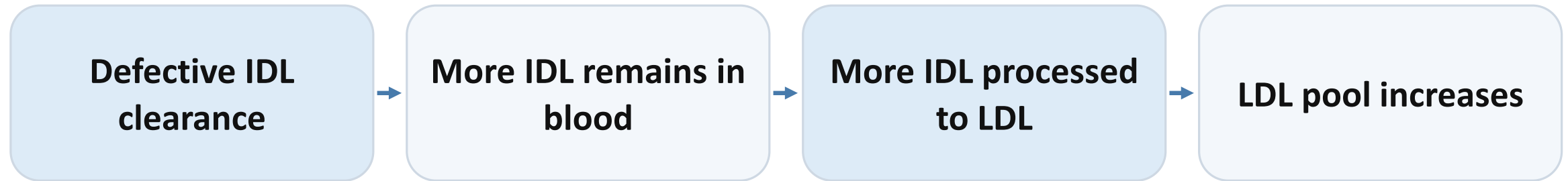
Normal hepatocyte

- Many functional LDL receptors
- Effective binding and internalization
- Continuous receptor recycling
- Lower circulating LDL

FH-affected hepatocyte

- Fewer effective LDL receptors
- Inadequate receptor-mediated uptake
- Slower LDL clearance
- Elevated circulating LDL

LDLR deficiency also increases LDL formation



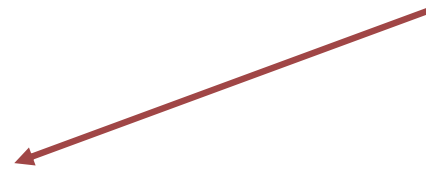
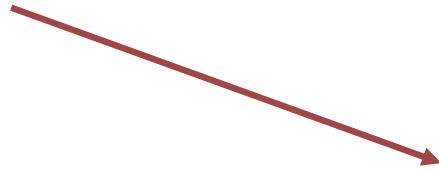
Elevated LDL is not solely failure of LDL uptake; Precursor diversion contributes.

The FH phenotype has two reinforcing components

**LDL clearance
Decreases**

**IDL → LDL
Conversion increases**

Circulating LDL rises



Normal and FH LDL trafficking compared

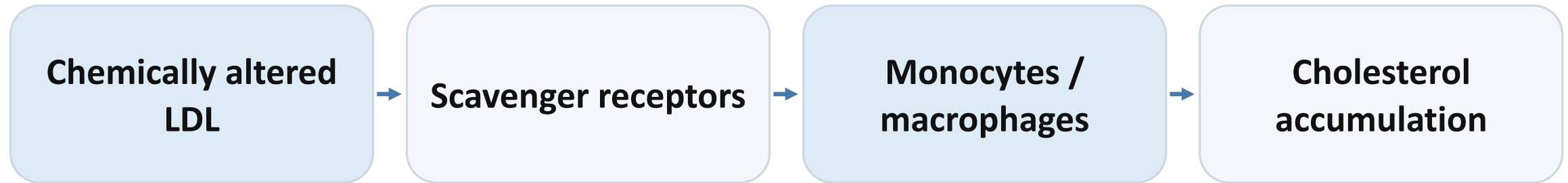
Normal LDL transport

- LDL binds LDLR
- Complex internalizes
- LDL is degraded
- Receptor returns to membrane

Familial hypercholesterolemia

- Receptor number or function is reduced
- LDL remains in circulation
- IDL clearance also falls
- Cholesterol accumulates in plasma

Modified LDL enters macrophages by scavenger pathways



Enhanced scavenger uptake in hypercholesterolemia.

Macrophage lipid loading contributes to xanthomas

- 1 Plasma LDL remains substantially elevated.
- 2 A portion of LDL undergoes chemical alteration.
- 3 Mononuclear phagocytes take up altered LDL via scavenger receptors.
- 4 Accumulated lipid contributes to xanthoma formation.

Xanthomas are a clinical manifestation of tissue cholesterol deposition.

Tendinous xanthomas are a hallmark of heterozygous FH

Textbook phenotype: Tendon xanthomas accompanying lifelong hypercholesterolemia.

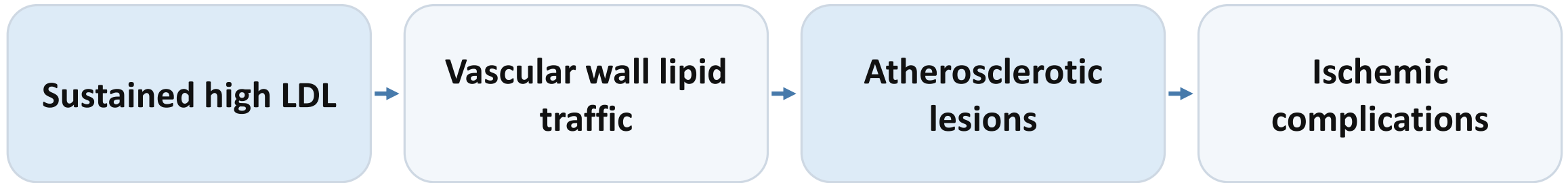
Clinicopathologic interpretation

Visible tendon lipid deposition reflects chronic excess cholesterol.

Presence increases suspicion for inherited LDL dysregulation.

Absence does not logically exclude molecular disease.

LDL excess accelerates atherosclerosis



Pathologic vascular consequences explain the importance of early detection.

Heterozygous FH often becomes evident in adult life

- 1 Lifelong elevation of plasma cholesterol begins at birth.
- 2 Tendon xanthomas may emerge with prolonged exposure.
- 3 Premature atherosclerosis develops over time.
- 4 Coronary complications become a major clinical concern.

Clinical recognition may occur long after the biochemical abnormality begins.

Severe biallelic FH can present in childhood

- 1 Very high LDL exposure starts early in life.
- 2 Skin xanthomas may appear at a young age.
- 3 Coronary, cerebral and peripheral vascular disease can develop early.
- 4 Myocardial infarction can occur before age 20.

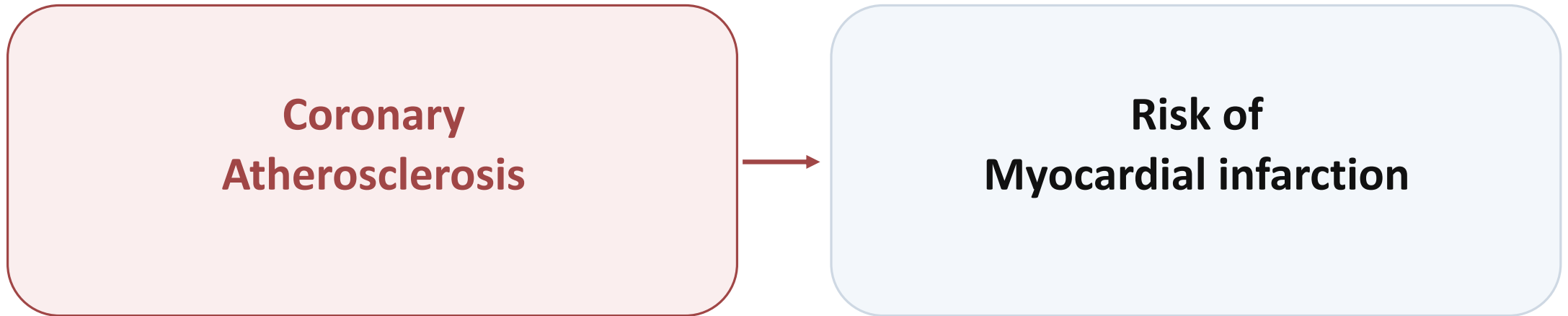
The earlier vascular phenotype reflects an extreme receptor-defect burden.

Clinical severity tracks the functional receptor deficit

Molecular background	Receptor activity	Expected phenotype
One affected LDLR allele	Reduced (~half normal receptors)	High LDL; premature adult disease
Two severely affected LDLR alleles	Virtually absent normal receptors	Marked LDL elevation; childhood disease
APOB ligand defect	Receptors poorly capture LDL	Elevated LDL via defective binding
PCSK9 activating variant	Receptors preferentially degraded	Elevated LDL via receptor scarcity

Premature myocardial infarction is the major warning

Persistent LDL elevation promotes premature vascular atherosclerosis.



FH among 3%–6% of survivors of myocardial infarction.

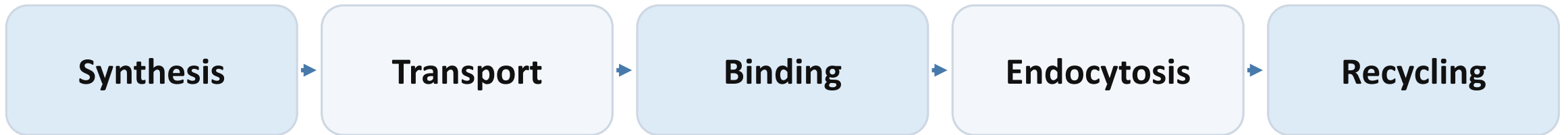
Lipid elevation should trigger an inherited-disease hypothesis

- 1 Recognize unusually high LDL cholesterol as a possible lifelong process.
- 2 Ask whether there is a family pattern of early vascular disease.
- 3 Assess visible tendon or skin xanthomas when present.
- 4 Consider the molecular mechanisms capable of impairing LDL clearance.

This is a mechanistic reasoning framework, not formal diagnostic criteria.

Class I LDLR mutations: No receptor synthesis

Defective step: Synthesis



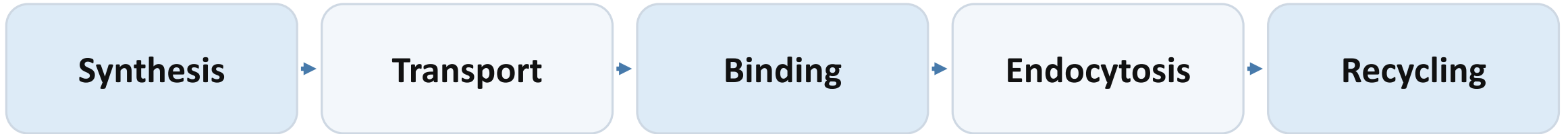
Class I: Failure of LDL receptor protein synthesis

A receptor is not produced and therefore cannot reach the cell surface.

Class I is relatively uncommon.

Class II LDLR mutations: Retention in endoplasmic reticulum

Defective step: ER-to-Golgi trafficking



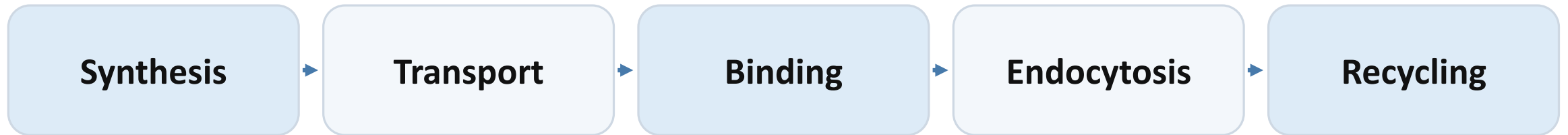
Class II: Mutant LDLR remains in the ER

Folding defects or truncations prevent normal transport to the Golgi.

Surface receptor availability is reduced despite attempted synthesis.

Class III LDLR mutations: Defective ligand binding

Defective step: Ligand attachment



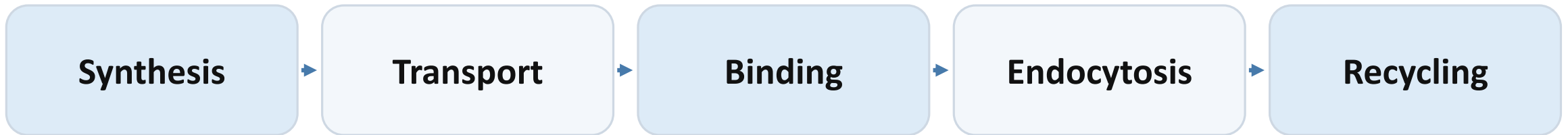
Class III: Mutant LDLR binds LDL poorly or not at all

Receptors reach the surface but have an ineffective ApoB-binding site.

Surface expression does not guarantee uptake.

Class IV LDLR mutations: Impaired coated-pit localization

Defective step: Internalization



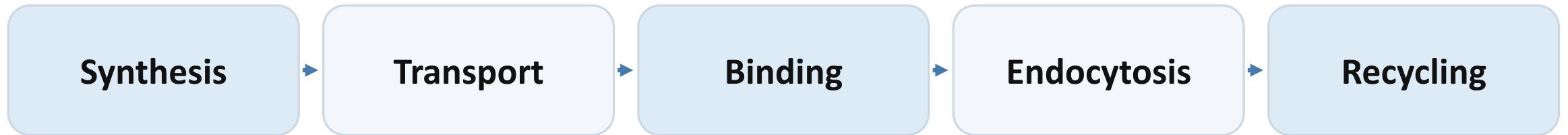
Class IV: Receptors fail to enter coated pits

Mutant receptors reach the surface and bind ligand normally.

Defective localization blocks uptake of receptor-bound LDL.

Class V LDLR mutations: Defective endosomal recycling

Defective step: Recycling



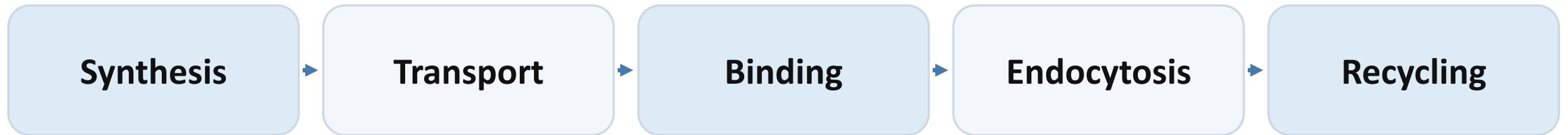
Class V: Ligand dissociation in the endosome fails

The receptor–LDL complex is diverted toward degradation rather than reuse.

LDL binding and initial internalization can remain intact.

Class VI LDLR mutations: Mistargeting at the hepatocyte surface

Defective step: Membrane targeting



Class VI: Receptor is missorted to the apical surface

Poor receptor availability at the sinusoidal interface impairs plasma LDL uptake.

Class VI was not depicted's original figure 5.9.

Functional classes I–VI of LDLR variants

Class	Defective operation	Functional consequence
I	Receptor synthesis	No LDLR protein
II	ER-to-Golgi trafficking	Intracellular retention
III	LDL / ApoB binding	Weak or absent ligand binding
IV	Coated-pit localization	Failed internalization
V	Endosomal dissociation/recycling	Reduced recycling
VI	Basolateral membrane targeting	Mislocalized surface receptor

Every LDLR class maps to one vulnerable transport step

- 1 Class I: Receptor never synthesized.
- 2 Class II: Receptor retained before reaching Golgi.
- 3 Class VI: Receptor fails to target the basolateral membrane.
- 4 Class III: Cell-surface receptor cannot bind LDL effectively.
- 5 Class IV: Receptor–LDL complex fails to enter coated pits.
- 6 Class V: Internalized receptor fails to recycle efficiently.

Transport sequence clarifies why all six classes produce LDL accumulation.

Case application: Altered ligand versus altered receptor

A person has inherited hypercholesterolemia. The LDL receptor is present at the hepatocyte membrane, but LDL particles bind inefficiently.

Which gene mechanism most directly explains defective ligand function?

APOB: Altered ApoB-100 reduces LDL binding to the receptor.

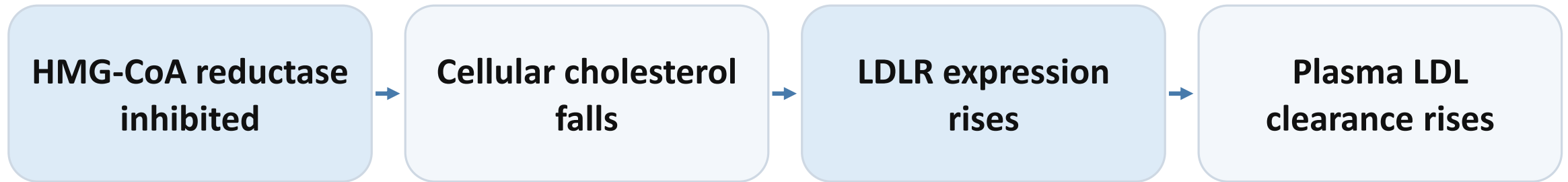
Case application: Preserved binding, failed internalization

Mutant LDL receptors appear on the cell surface and bind LDL normally, but receptor-bound LDL is not effectively internalized.

Which class of LDLR functional defect is implicated?

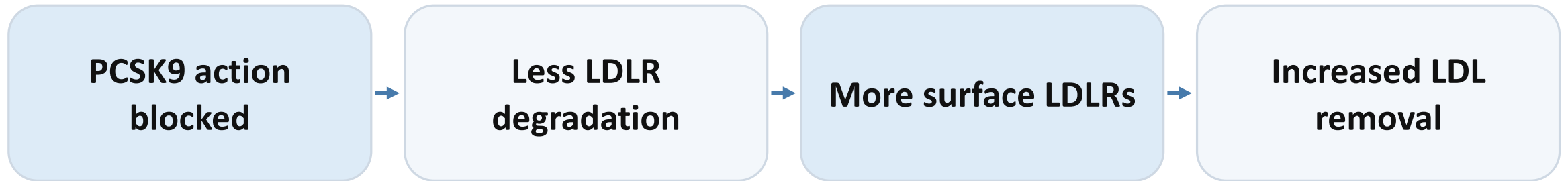
Class IV: Defective coated-pit localization and endocytosis.

Statins decrease intracellular cholesterol synthesis



Statin benefit includes increased hepatocyte surface LDL receptors.

PCSK9 inhibition preserves LDL receptor recycling



The intervention acts on receptor turnover rather than ApoB synthesis.

Natural PCSK9 loss of function validates its biology

- 1 PCSK9 was implicated through individuals with very low serum cholesterol.
- 2 These individuals carried loss-of-function PCSK9 variants.
- 3 Reduced PCSK9 activity permits increased availability of LDL receptors.
- 4 The observation supported development of PCSK9-targeted treatment.

Human genetic variation helped expose a therapeutically actionable mechanism.

Two therapeutic mechanisms increase effective LDLR availability

Strategy	Initial molecular target	Effect on LDLR	Result
Statin	HMG-CoA reductase	Increased receptor synthesis	Greater LDL clearance
PCSK9 inhibition	PCSK9-mediated degradation	Reduced receptor destruction	Greater LDL clearance

Both mechanisms rely on functional receptor-mediated LDL disposal.

Molecular phenotype predicts pathway dependence

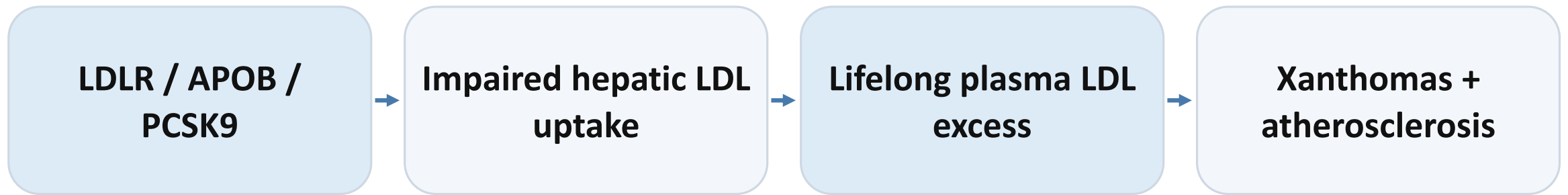
Relevant question

- Is receptor synthesis retained?
- Can the receptor reach the correct surface?
- Does it bind LDL?
- Can it internalize and recycle?

Implication

- Therapies that raise receptor abundance require usable LDLR function.
- A near-null receptor state differs mechanistically from partial receptor function.
- Variant class gives biological context—not a treatment prescription.

Integrated pathogenesis: From gene to vascular disease



FH exemplifies how a single molecular pathway produces multisystem pathology.

Five essential concepts to retain

- LDLR-dependent hepatic removal governs plasma LDL exposure.
- LDLR, APOB and PCSK9 defects converge on impaired LDL clearance.
- LDLR deficiency diverts IDL toward LDL and slows LDL disposal.
- Six LDLR classes correspond to different cellular transport failures.
- Xanthomas and premature atherosclerosis follow sustained LDL excess.

References and source limitations

Primary teaching source

Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. (2026). Chapter 5, “Genes and Human Diseases,” pp. 127–134.

Scope and verification

- Prepared from the supplied Robbins Markdown text and topic archive.
- Original chapter PDF and textbook figures were not available for page-image verification.
- Diagrams are newly authored PowerPoint schematics, not reproduced textbook figures.
- Clinical diagnostic criteria and current treatment guidelines are deliberately outside this source-derived lecture.