Familial Hypercholeterolaemia

Is it all about statins?

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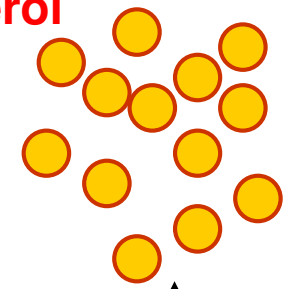
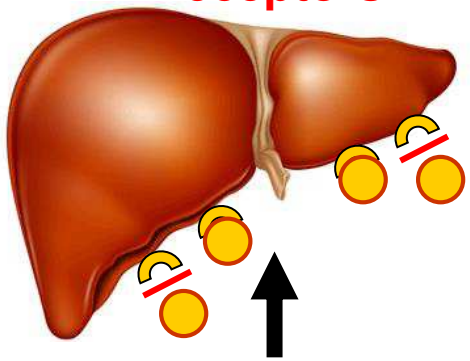
***ACRA**, 8th August 2017*

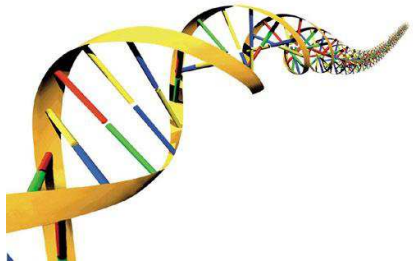
Elevated LDL cholesterol



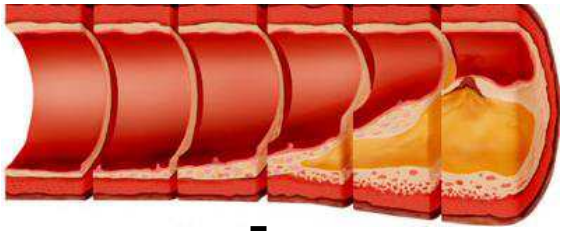
Liver with only **50% functional LDL receptors**

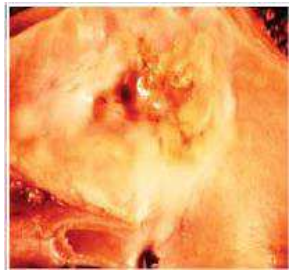


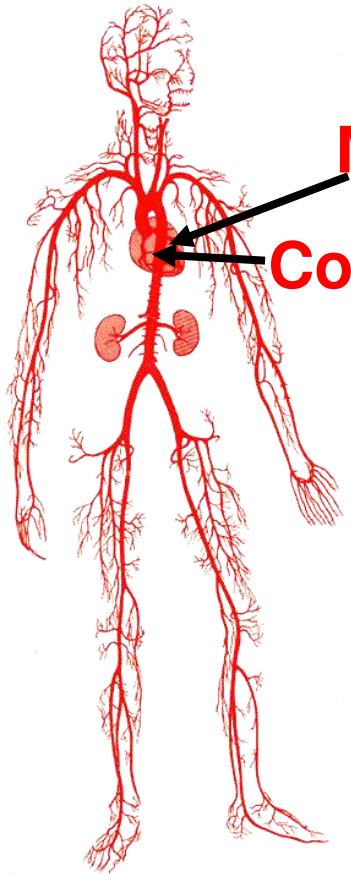
Mutations in LDL receptor, apolipoproteinB or PCSK9



Atherosclerosis

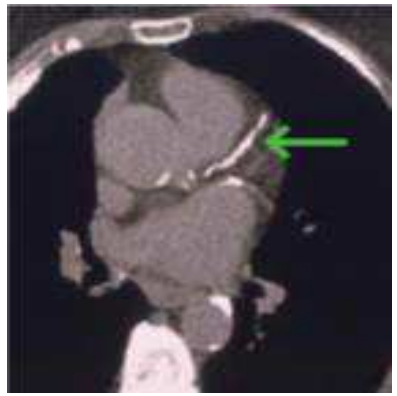






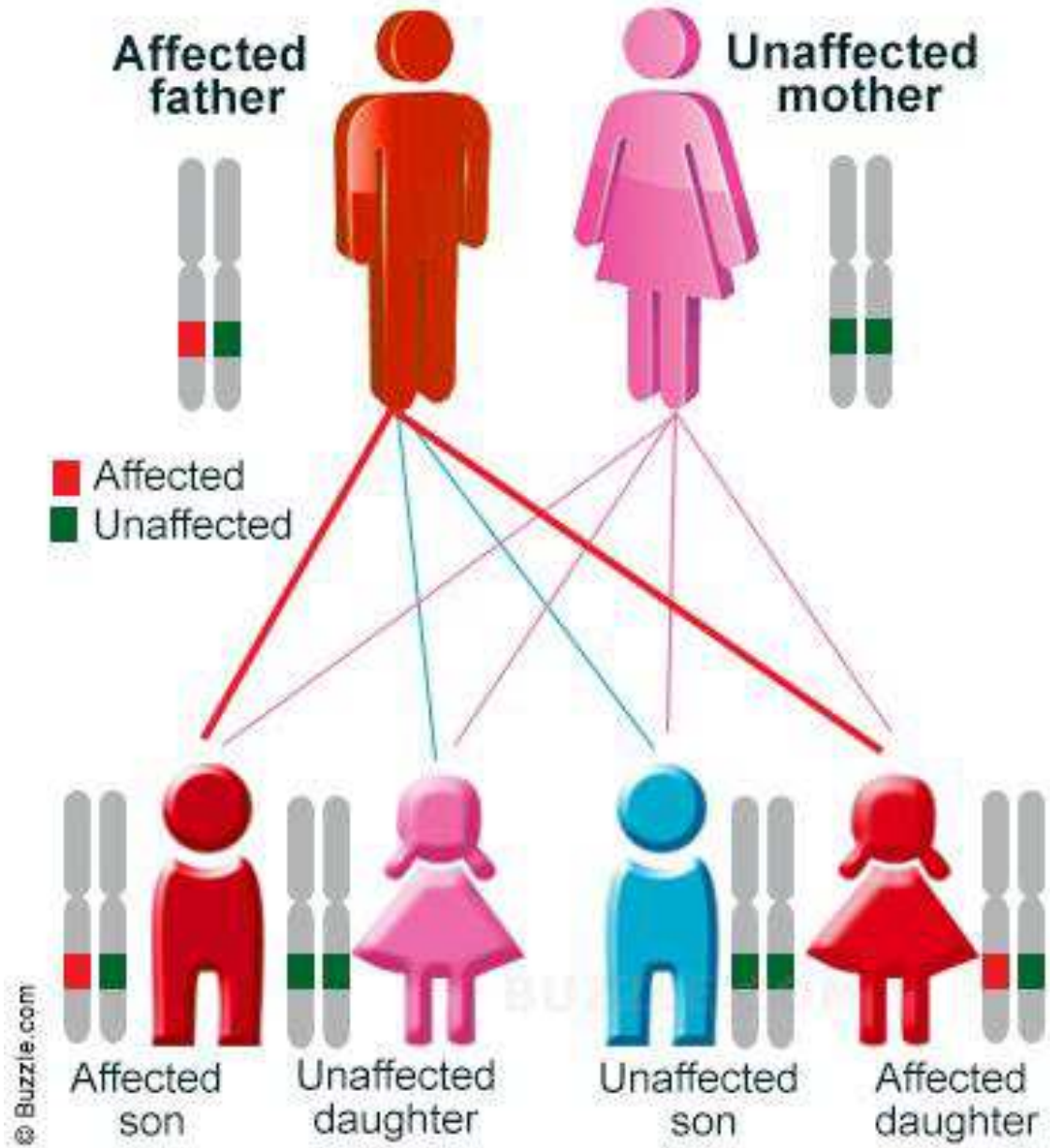
Myocardial infarction

Coronary heart disease



At least 1 in 300 people have FH

De Ferrante Circ 2016, Benn EHJ 2016, Wald NEJM 2016, Do Nature 2015, Futema Athero 2017, Abul-Husn Science 2016, Khera J Am Coll Cardiol 2016, Watts Int J Cardiol 2015, Shi Int J Cardiol 2014


Affected father
Unaffected mother
Affected
Unaffected
Affected son
Unaffected daughter
Unaffected son
Affected daughter
© Buzzle.com

Typical Features of FH

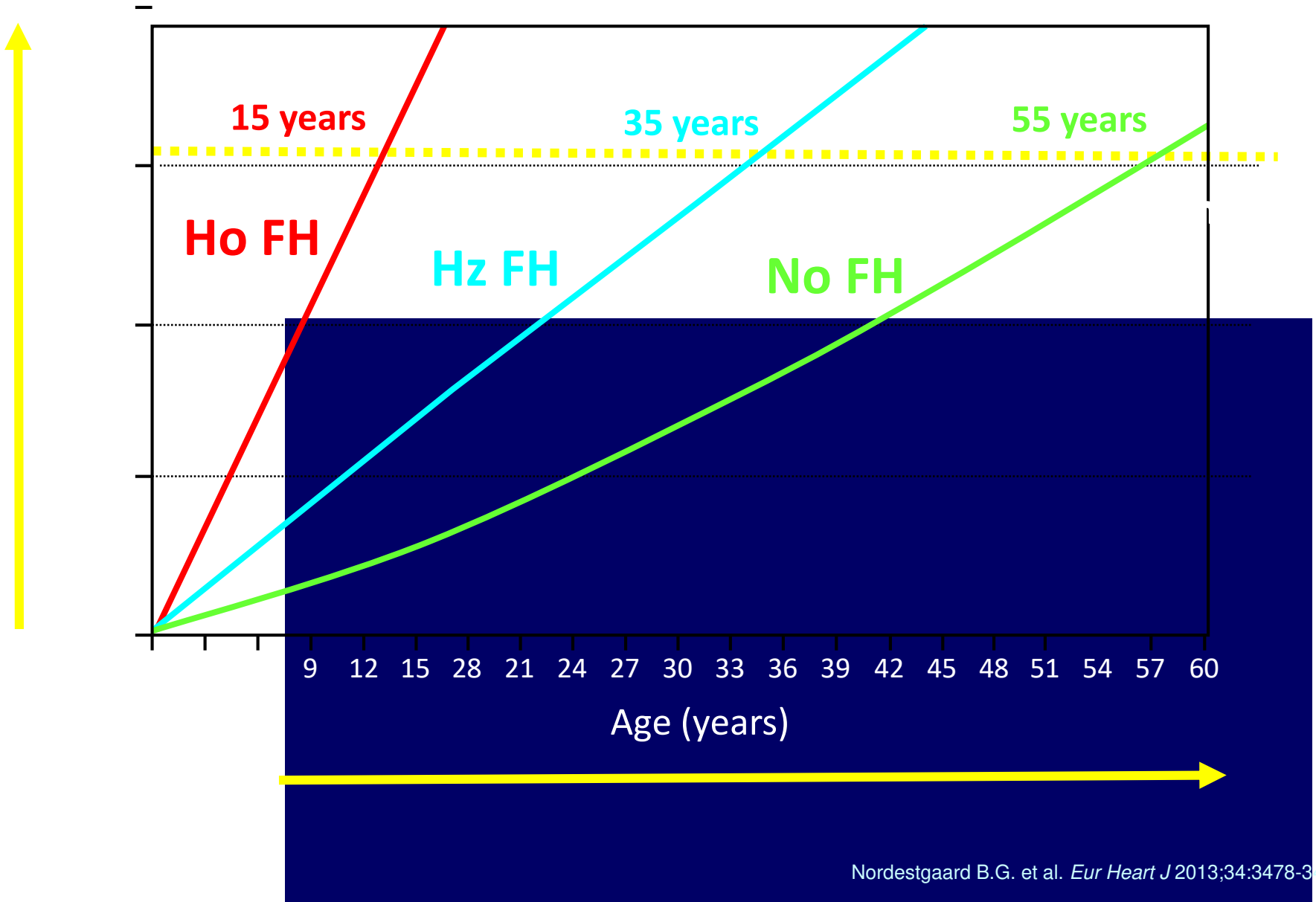
Heterozygous FH

-
-
-
-

Homozygous FH

-
-
-
-

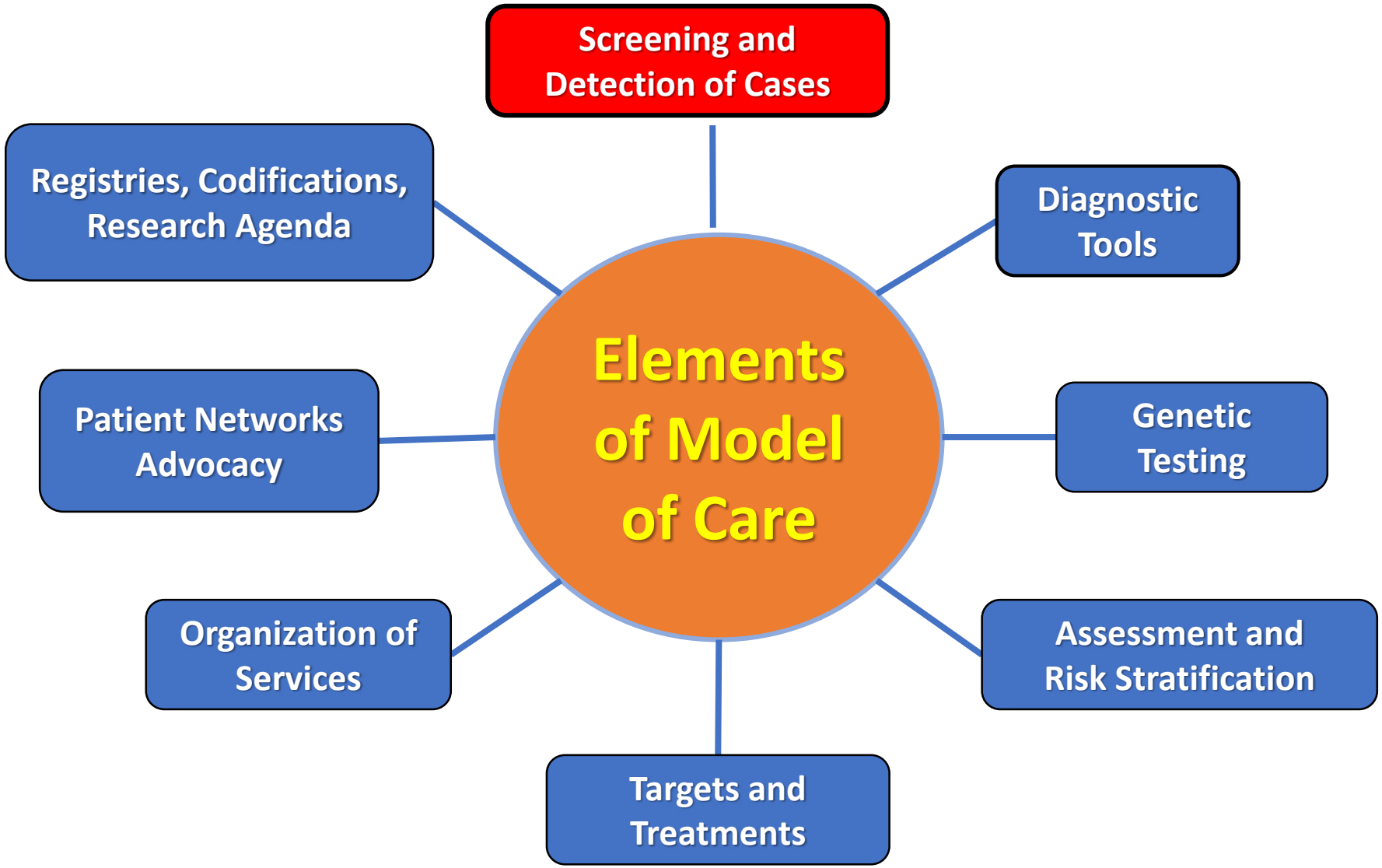
LDL-Cholesterol Life-Years and CAD in FH



Nordestgaard B.G. et al. *Eur Heart J* 2013;34:3478-3490

Several Gaps in Care

Anatomy of Care for FH

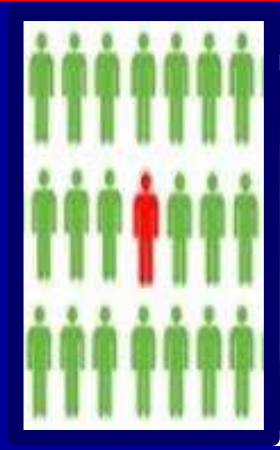


Why Screen for FH ?

- Serious consequences from youth
- Absent signs and symptoms in young
- Good tests
- Good therapy
- Cost-effective
- Responsibility

Screening: Where, Who, How ?

- Coronary Care
- Primary Care
- Laboratory Medicine
- Cascade Screening



Martin et al Curr Opin Lipidol 2017 April 19th on-line

Diagnosis

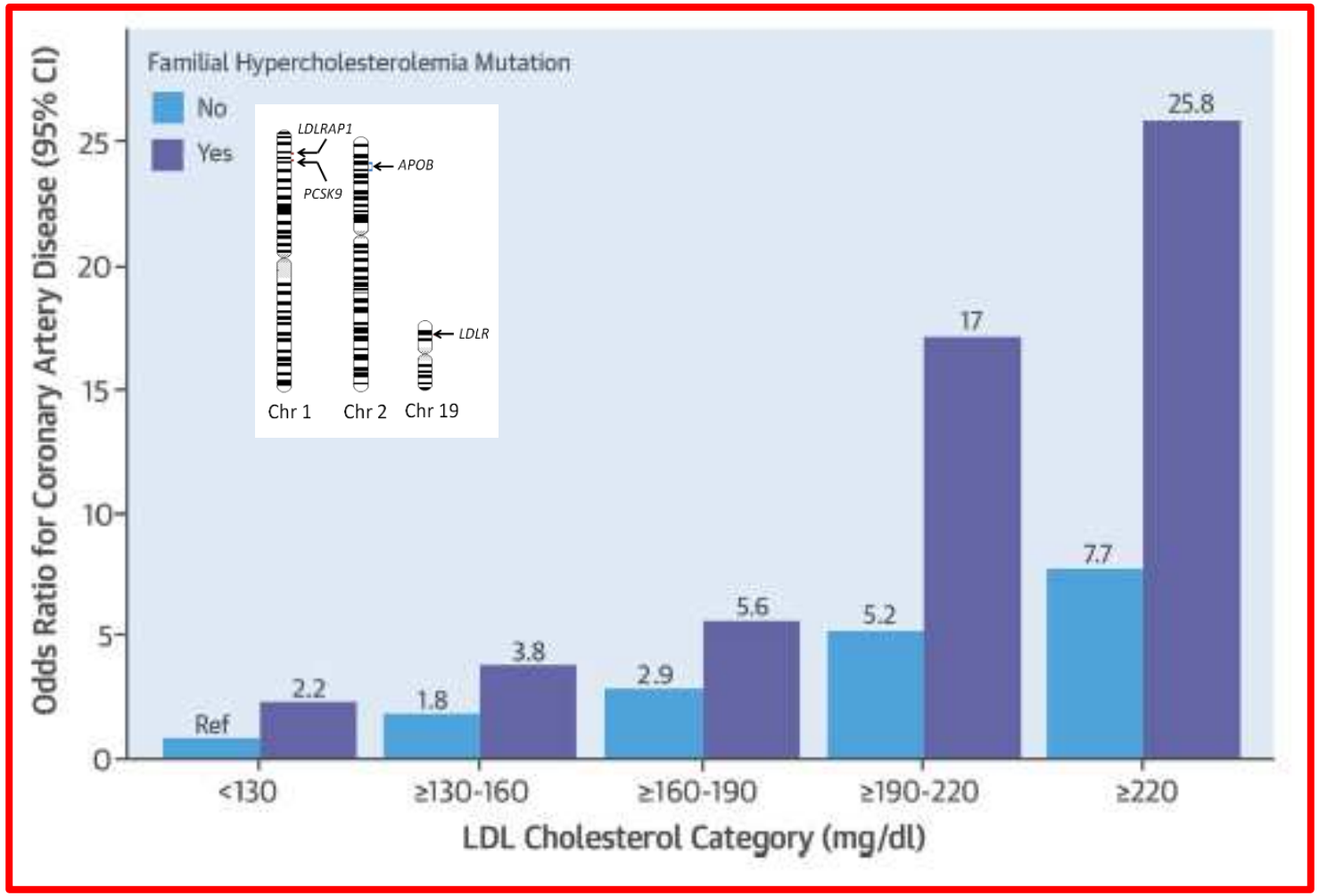
FH
high LDL
family history of CVD/high choL
physical signs
high FH score

FH Criteria	Score
Family history	
First-degree relative with known premature coronary and/or vascular disease (men aged <55 years, women aged <60 years) OR with known LDL-cholesterol above the 95th percentile for age and gender	1
First-degree relative with tendinous xanthomata and/or arcus cornealis OR Children aged <18 years with LDL-cholesterol above the 95th percentile for age and gender	2
Clinical history	
Patients with premature coronary artery disease (men aged <55 years, women aged <60 years)	2
Patients with premature cerebral or peripheral vascular disease (men aged <55 years, women aged <60 years)	1
Blood Test	
LDL-cholesterol (mmol/L)	LDL-C ≥8.5	8
	LDL-C 6.5–8.4	5
	LDL-C 5.0–6.4	3
	LDL-C 4.0–4.9	1

FH	Total score
Definite	>8
Probable	6-8
Possible	3-5
Unlikely	<3

Do you need to do genetic testing ?

Value of Sequencing FH Genes in Patients with very High Cholesterol

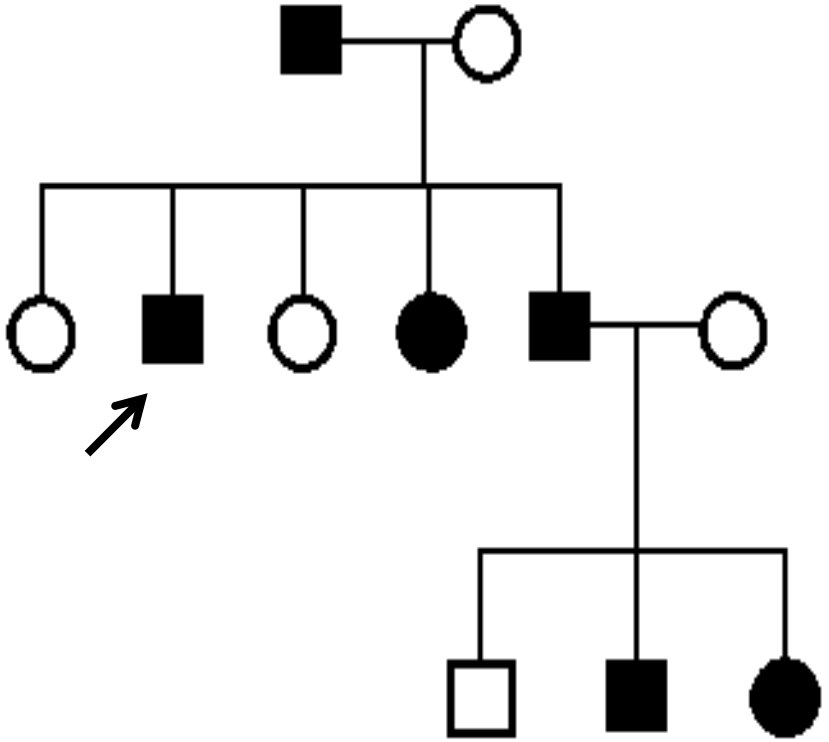


Khera et al J Am Coll Cardiol 2016; 67: 2578-90

Cascade screening is about families; you start with identifying the index case.

Family Cascade Screening

Relative	Prevalence
1st degree	50%
2nd degree	25%
3rd degree	12.5%
General Population	0.2 % or 1 in 500

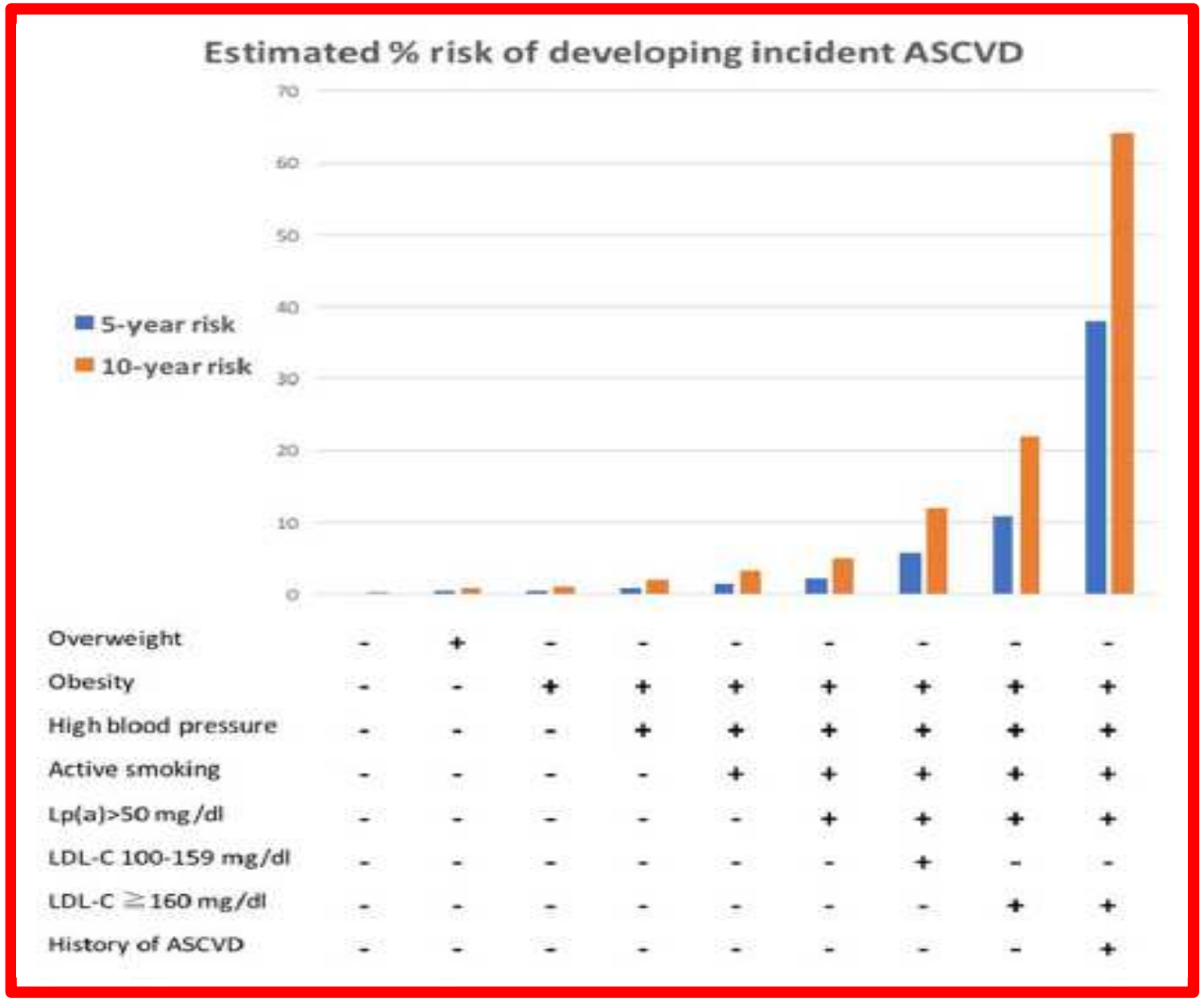


Screening principle

1 FH patient → >4 new FH

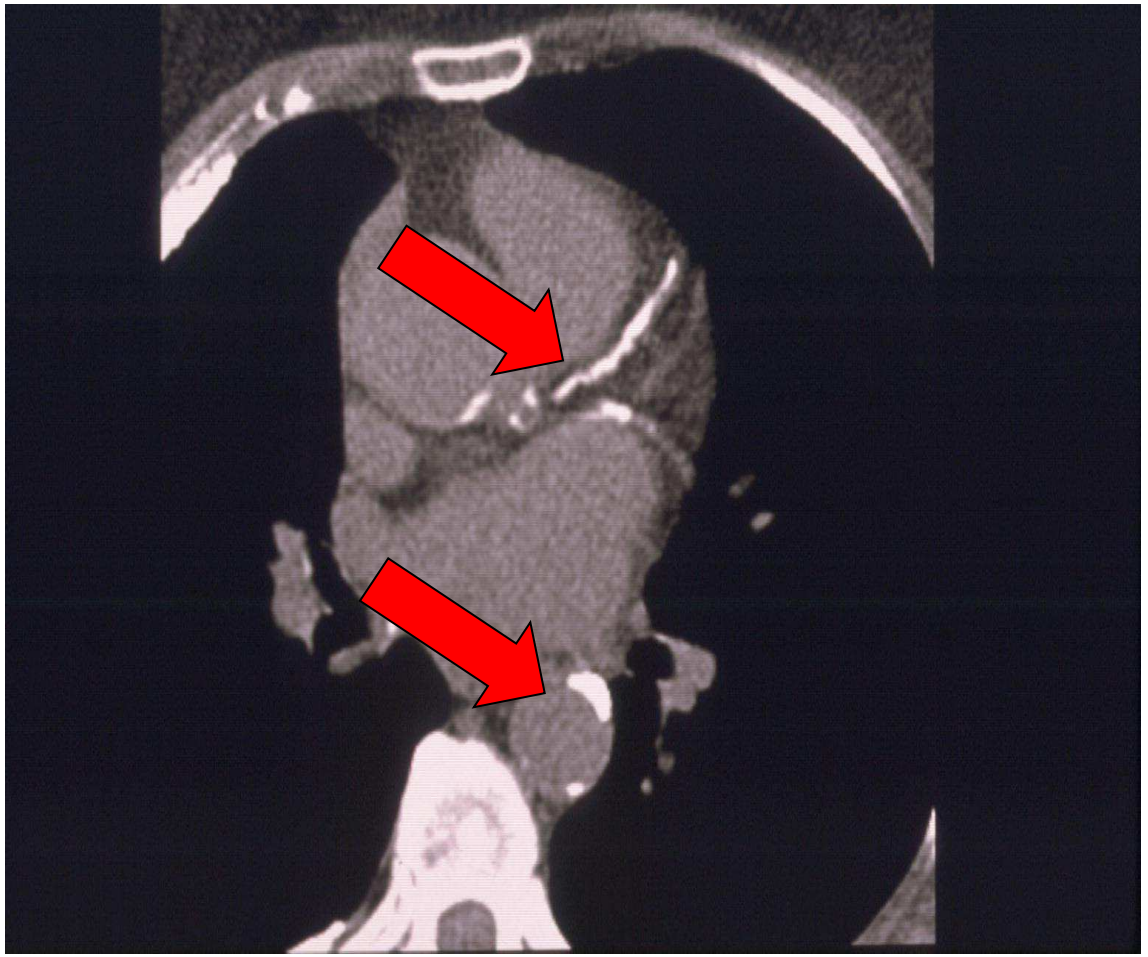
Predicting CVD Events in FH

The SAFEHEART Registry



Perez de Isla et al Circulation 2017; 135: 2133-44

Coronary Artery Calcium in FH



3 Principles for LDL lowering in FH

Treatment Options

Heart healthy diet

Established Drugs

Niacin

New Drugs:

ApoB ASO, MTPI

Radical Therapies:

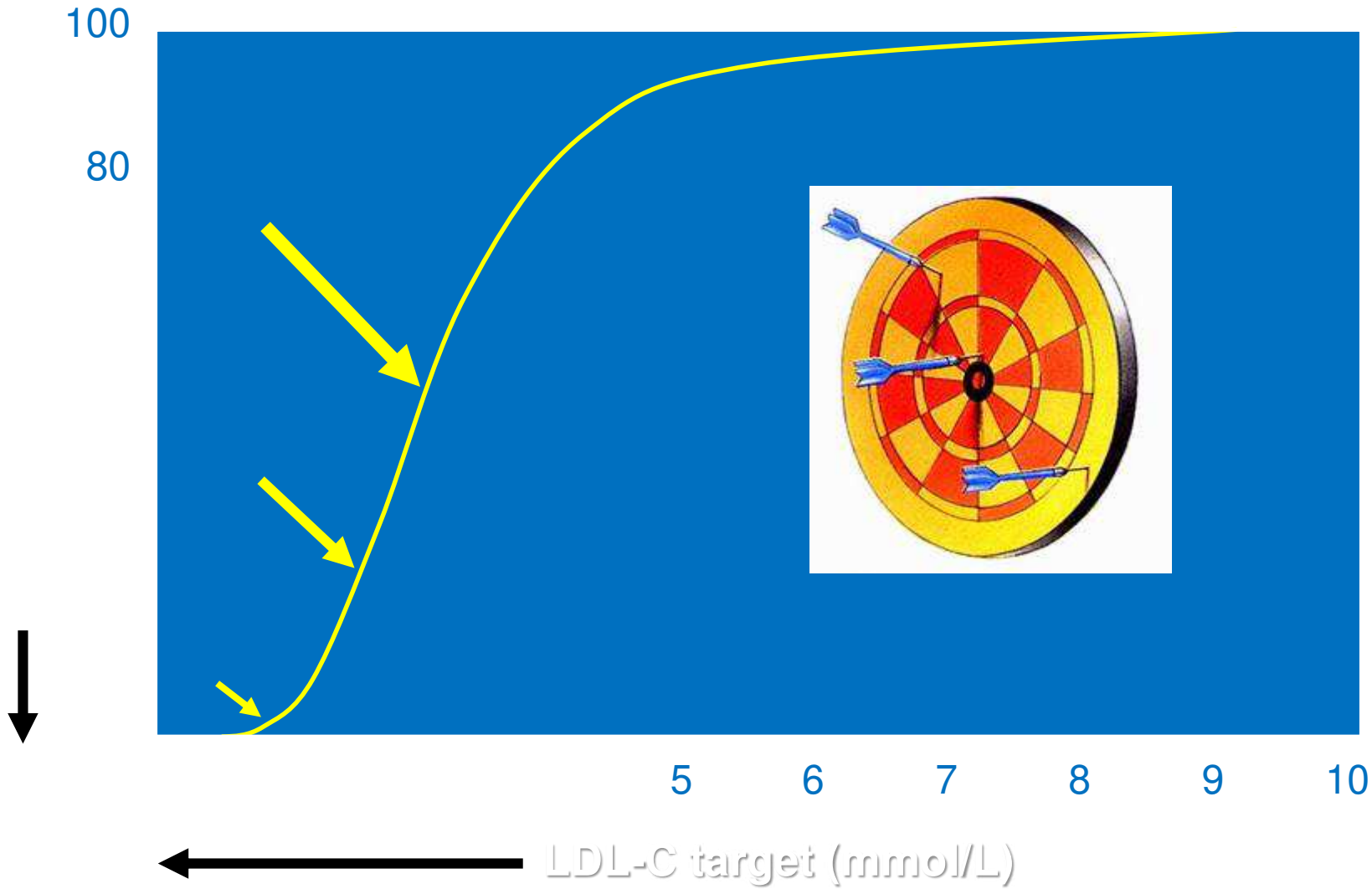
Liver Transplant

Management of Adult FH

- Lifestyle modifications; address all risk factors
- At least 50% reduction in plasma LDL cholesterol and then target >>
  - LDL cholesterol < **2.5** mmol/L (No CVD or other risk factors)
  - LDL cholesterol < **1.8** mmol/L (CVD or other risk factors)

Watts et al International Journal of Cardiology 2014

Proportion of FH patients who reach LDL-C targets on therapy

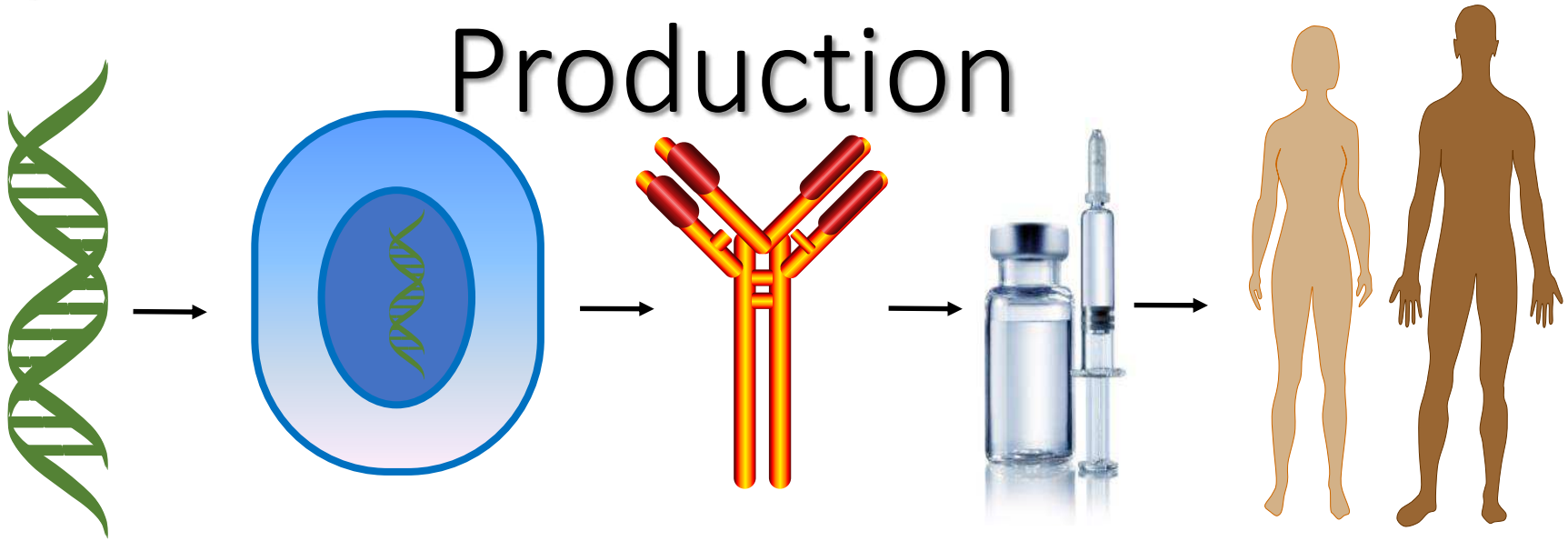


Pijlman AH Atherosclerosis 2010;209:189-94

New LDL Lowering Therapies

- PCSK-9 Inhibitors

Fully Human Monoclonal Antibody Production



Monoclonal antibody gene

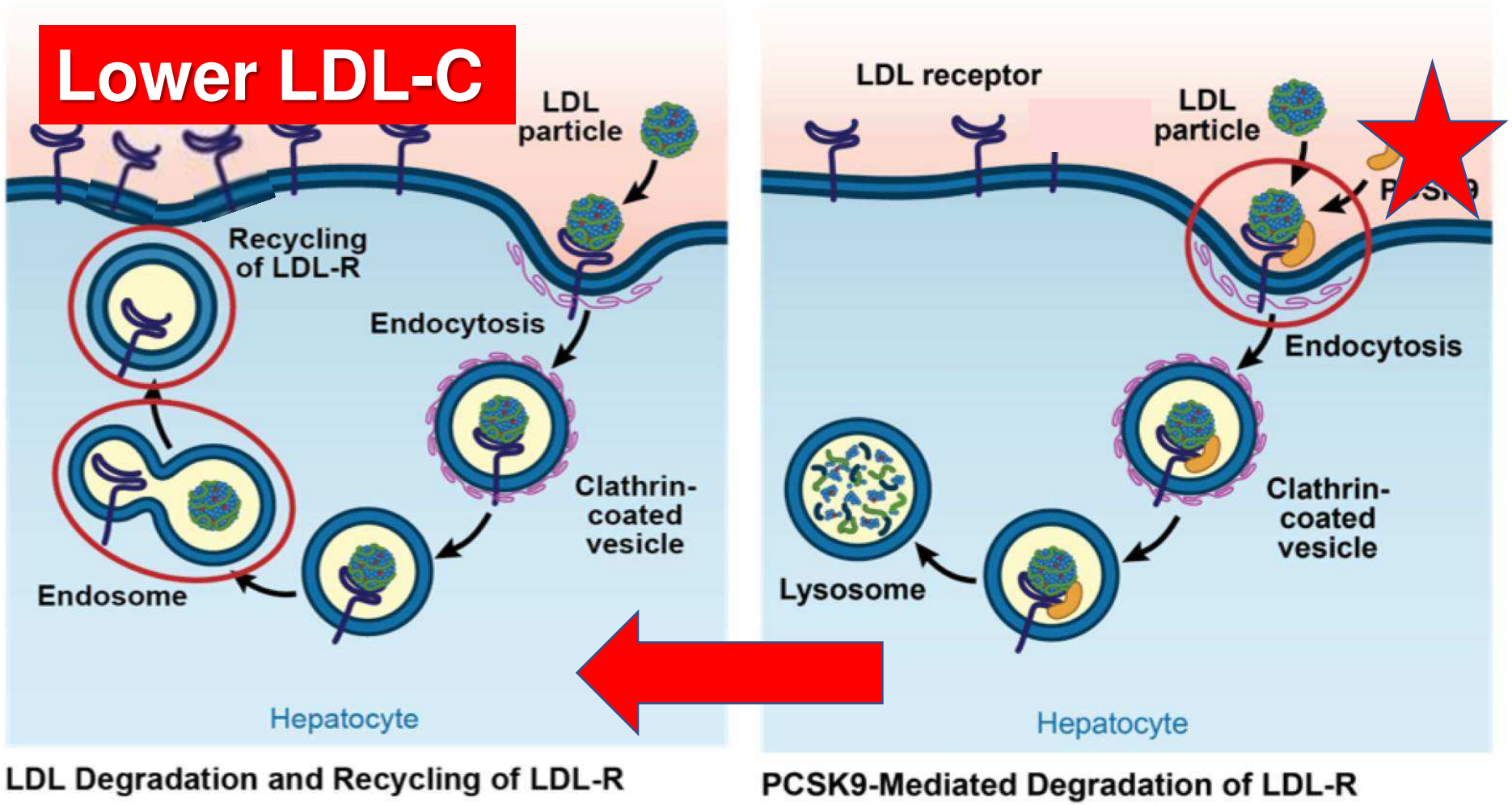
Manufacturing cell

Therapeutic monoclonal antibody

Final product

Patients

PCSK9 Inhibition Using Monoclonal Antibodies

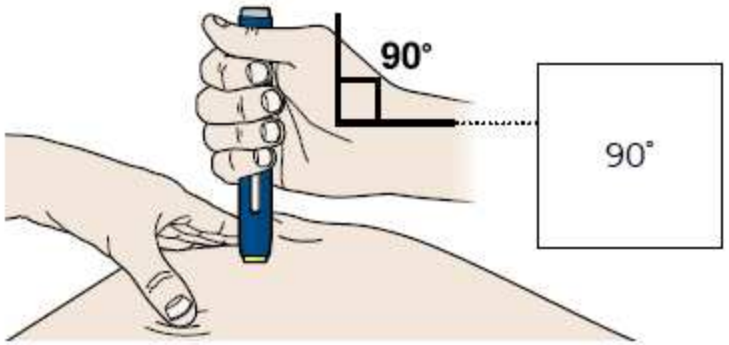


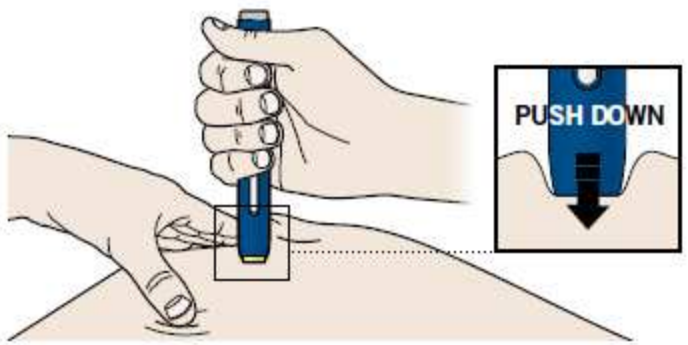
LDL Degradation and Recycling of LDL-R

PCSK9-Mediated Degradation of LDL-R

Lambert G, et al. *J Lipid Res*. 2012;53:2515-2524.

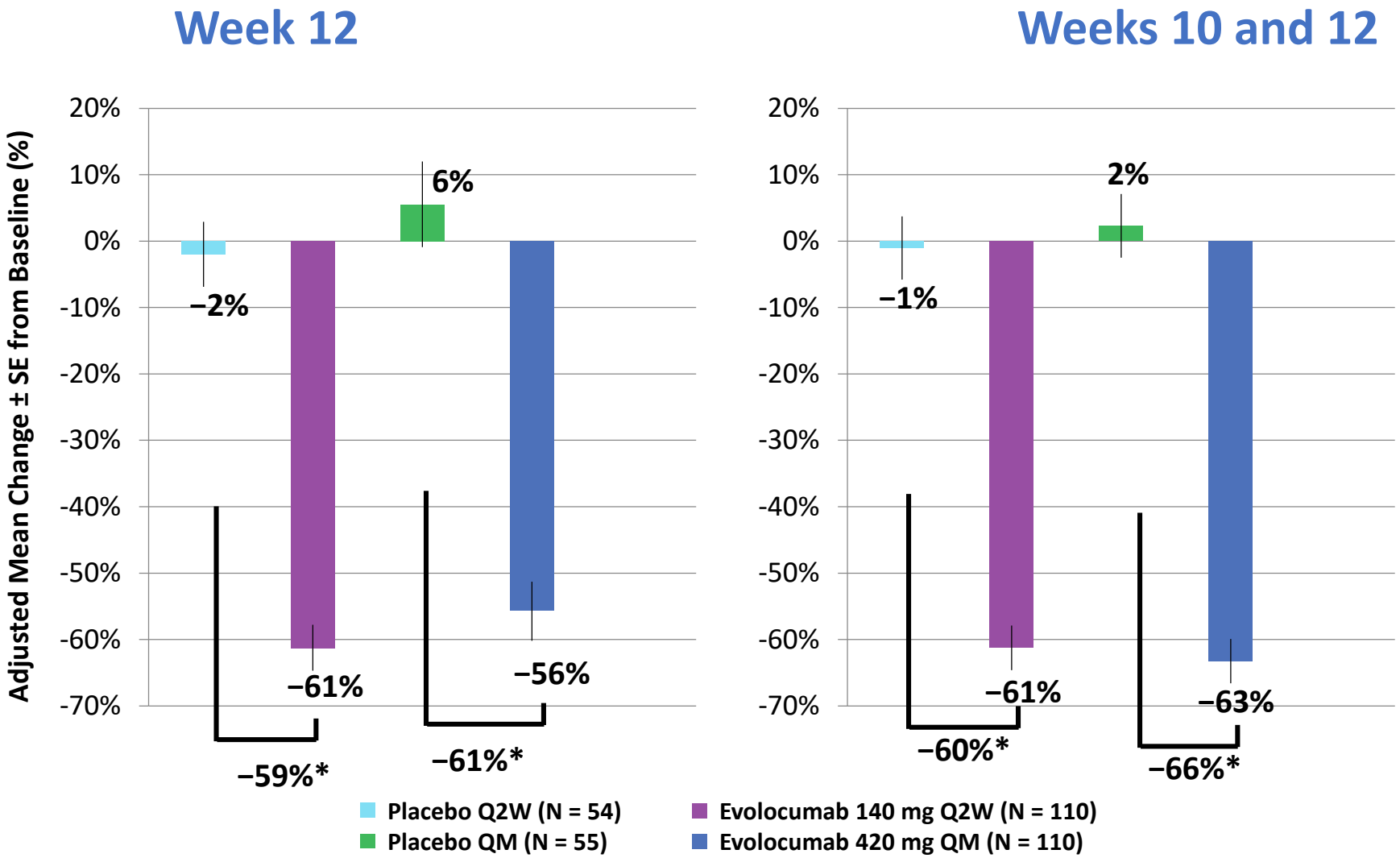
PCSK9 mAb SC injection Q2W





RUTHERFORD-2

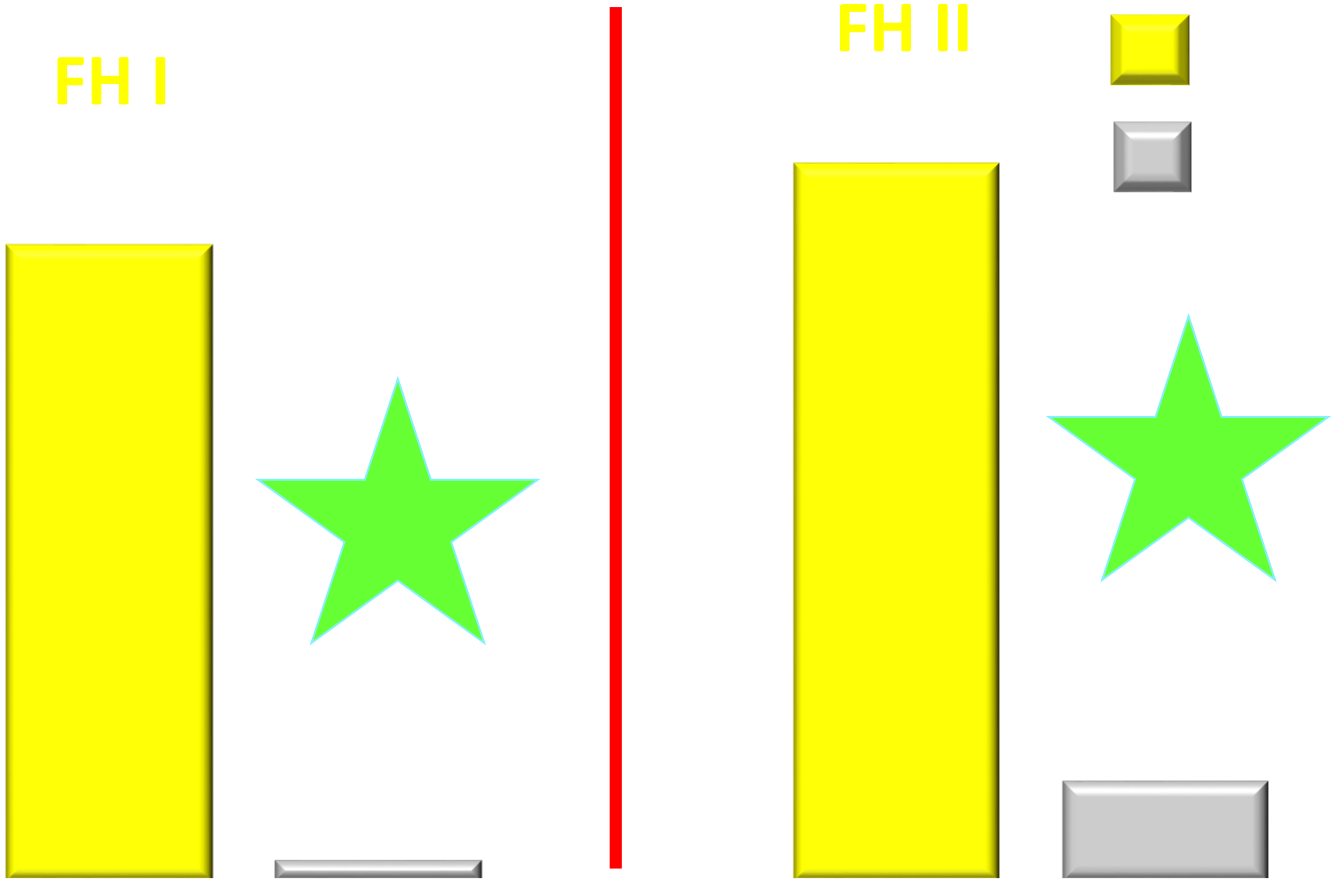
Mean % change in LDL-C from baseline in Heterozygous FH



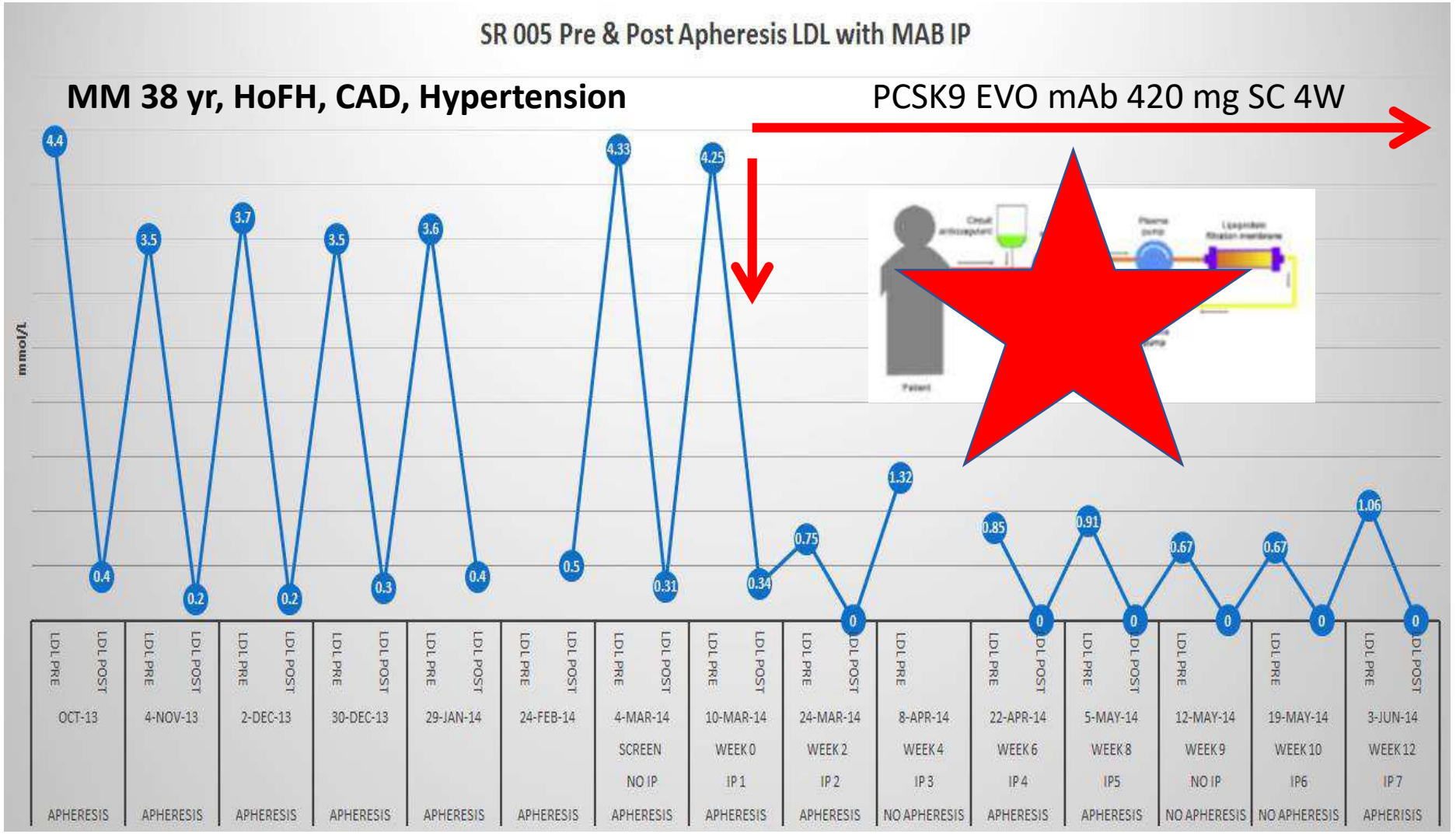
*P<0.0001 evolocumab treatment difference vs placebo

Raal FJ, et al. Lancet 2014; doi.org/10.1016/S0140-6736(14)61399-4.

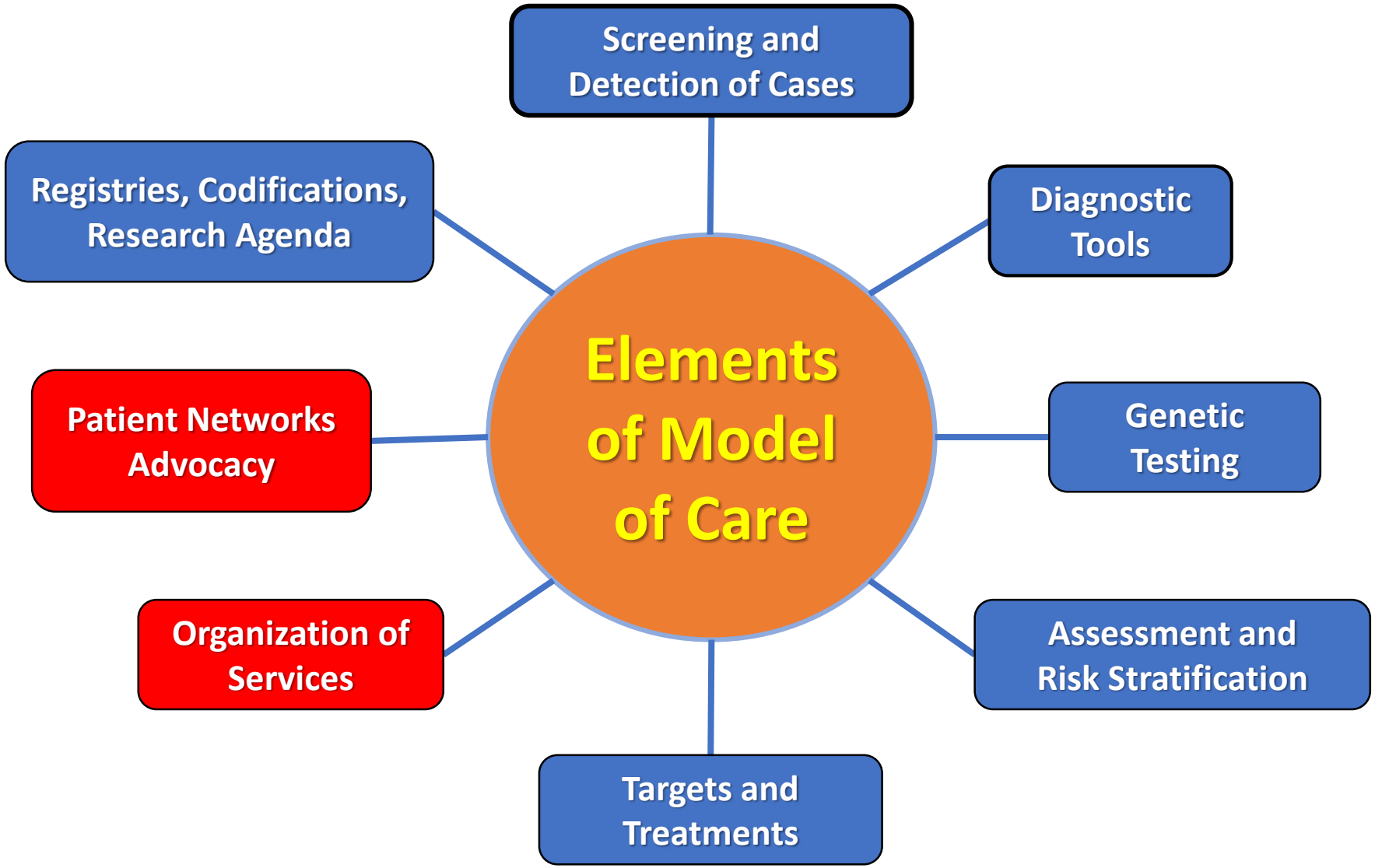
Most heFH Patients Receiving Alirocumab on Background Statin ± Other LLT Achieved LDL-C Goals



Effect of PCSK9 mAb on LDL-C while on Apheresis



Anatomy of Care



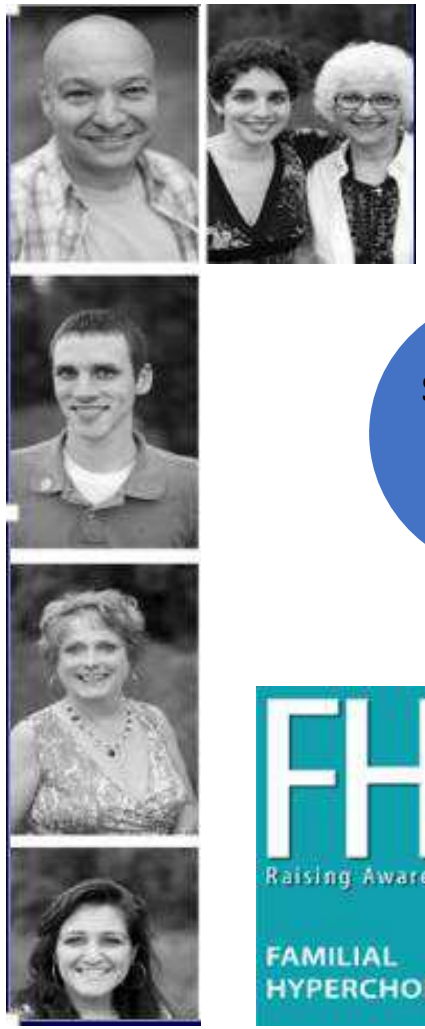
Organization of Care

- ~~Design model of care in context~~
- Multidisciplinary services, integrated with primary care:

Cardiology
Paediatric
Genetics
Imaging
Transfusion Medicine

Nursing
Dietetics
Psychology
Pharmacy
Pathology

Patient Support Groups and Networks

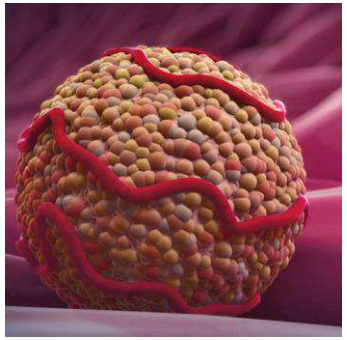


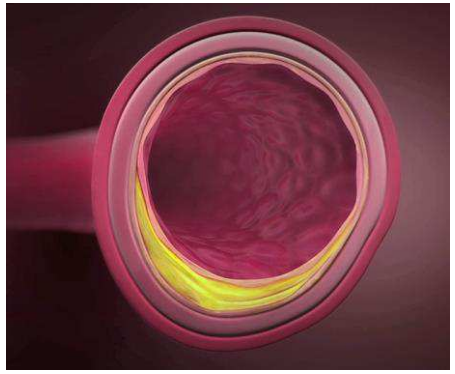
- Awareness raising
- Share/learn from each other
- Empower FH Patient Advocates
- Co-operate medical / science world
- Lobby for change

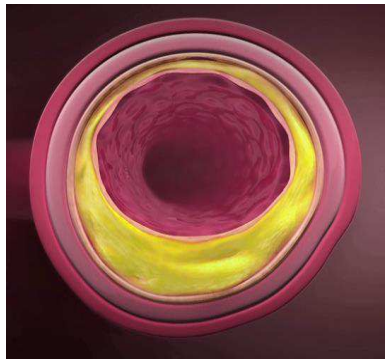
FH FOUNDATION
Raising Awareness. Saving Lives.
FAMILIAL HYPERCHOLESTEROLEMIA

FH Europe
The European FH Patient Network

FH is the most potent hidden risk factor for premature CAD in families







7 Take Home Messages about FH

High cholesterol > 7 mmol/L

Premature CAD, LDL receptor defect

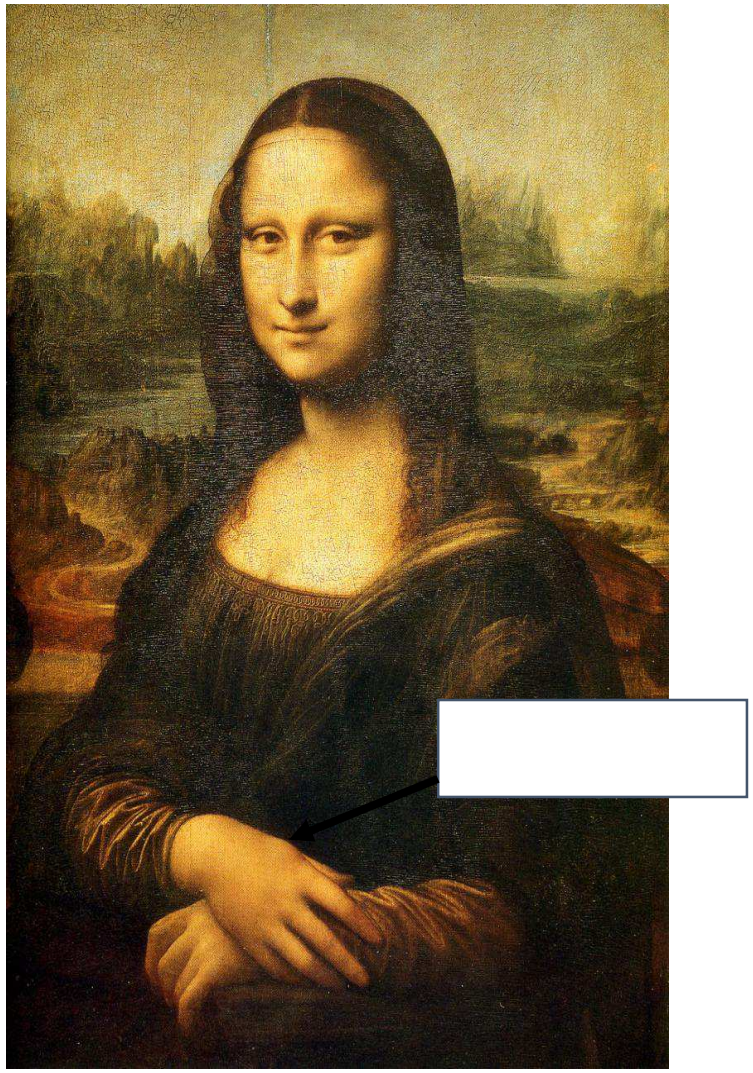
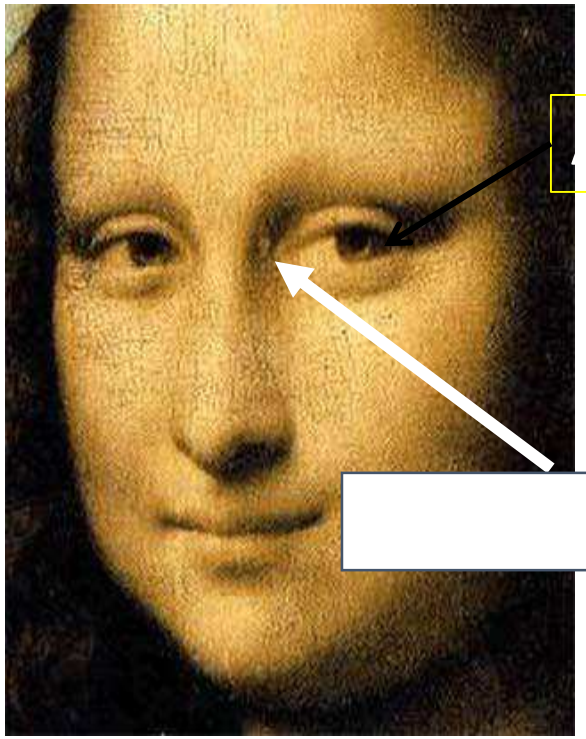
Prevalence at least 1:300

Dominant genetics: *'goes down the line'*

Screen and diagnose EARLY

Treat EARLY to LOW LDL-C target

PCSK9 inhibition gets to target

Who was this Person ?

Dequker et al *Medical Archaelogy 2004*