Detection and Treatment of FH

Closing the Gaps in Care

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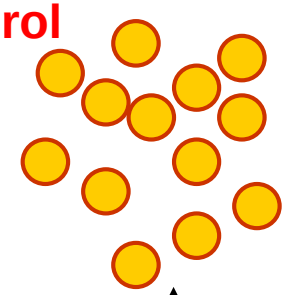
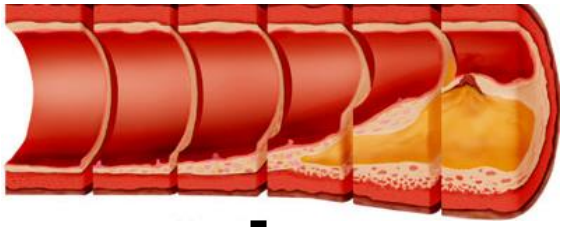
SITeCS, Naples, November 18th , 2018

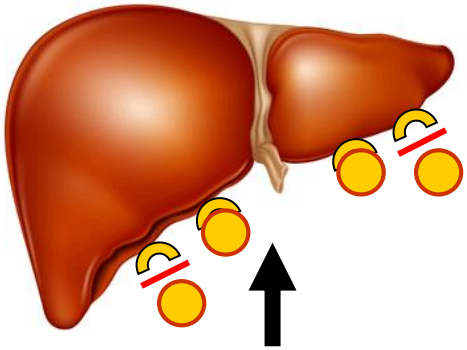
Elevated blood LDL cholesterol



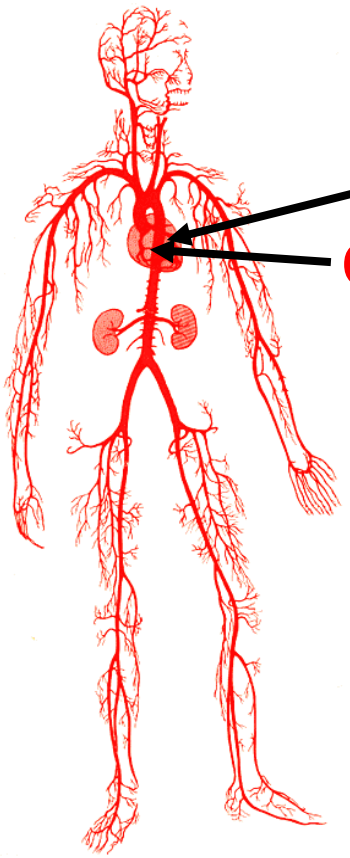
Atherosclerosis



Liver with only **50% LDL receptors that work**



Gene error in LDL receptor

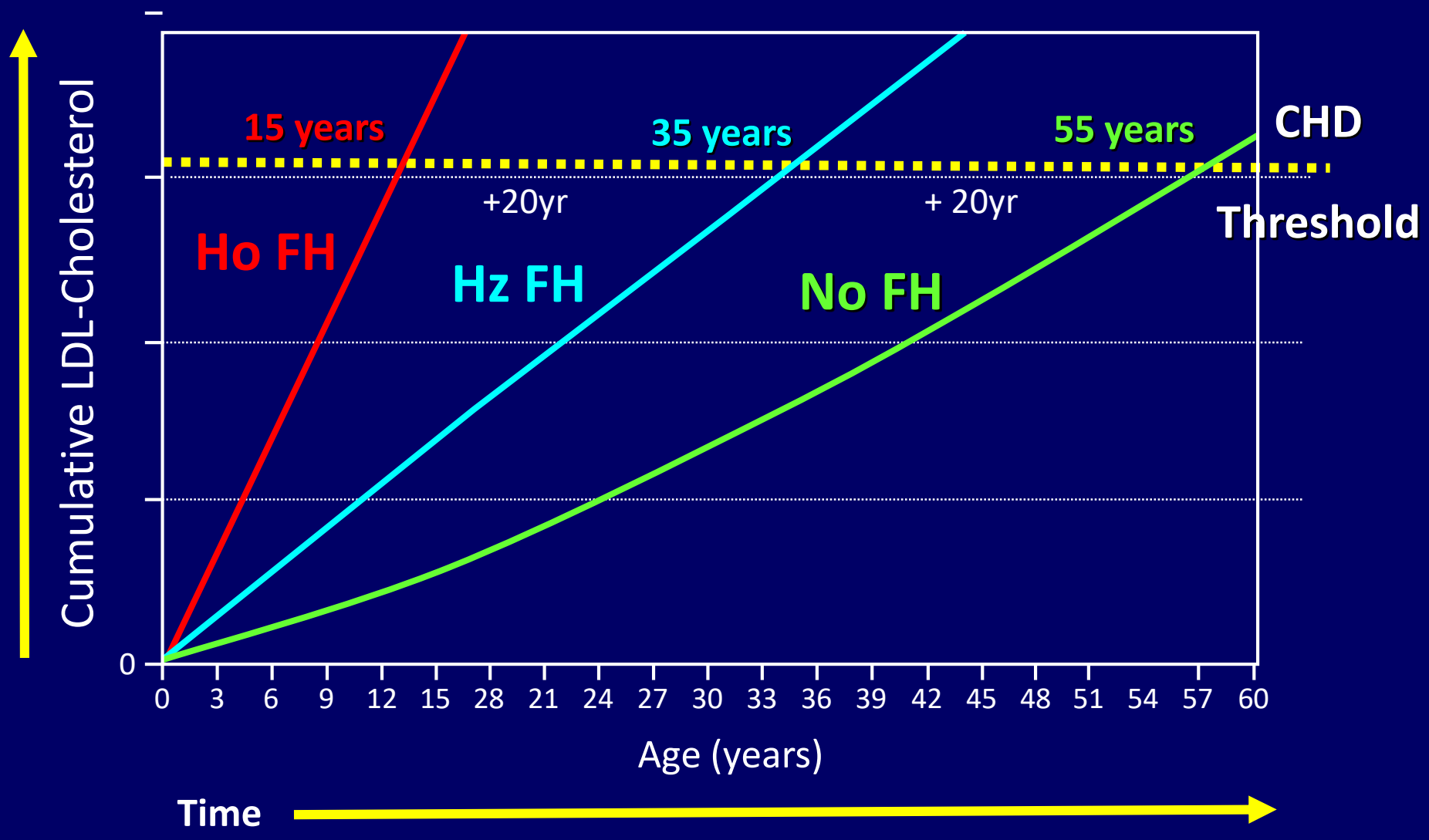


Heart attack

Coronary disease

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

LDL-Cholesterol and CHD Threshold in FH



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

Several Gaps in Care

European Heart Journal
doi:10.1093/eurheartj/eht273

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

Børge G. Nordestgaard[1*], M. John Chapman[2*†], Steve E. Humphries[3†],
Henry N. Gin
Robert A. He
Raul D. Santo
Petri T. Kovan
Alberico L. Ca
Anton F. H. St
Anne Tybjærg

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

Integrated guidance on the care of familial hypercholesterolaemia fro the International FH Foundation

Gerald F. Watts [a,*], Samuel Gidding [b,c], Anthony S. Wierzbicki [d], Peter P. Toth [e,f], Rodrigo
W. Virgil Brown [h], Eric Bruckert [i], Joep Defesche [j], Khoo Kah Lin [k], Michael Livingston [l], Pe
Klaus G. Parhofer [n], Frederick J. Raal [o], Raul D. Santos [p], Eric J.G. Sijbrands [q], William G. Si
kov [t], Brian Tomlinson [u], Albert Wiegman [v],
stelein [y]

AHA Scientific Statement

The Agenda for Familial Hypercholesterolemia

A Scientific Statement From the American Heart Association

Samuel S. Gidding, MD, FAHA, Chair; Mary Ann Champagne, RN, MSN, FAHA;
Sarah D. de Ferranti, MD, MPH; Joep Defesche, PhD; Matthew K. Ito, PharmD;
Joshua W. Knowles, MD, PhD, FAHA; Brian McCrindle, MD, MPH, FAHA;
Frederick Raal, MD, PhD; Daniel Rader, MD, FAHA; Raul D. Santos, MD, PhD;
Maria Lopes-Virella, MD, PhD, FAHA; Gerald F. Watts, DSc, MD, PhD;
Anthony S. Wierzbicki, MD, PhD, FAHA; on behalf of the Am
Atherosclerosis, Hypertension, and Obesity in the Young Committee o
Disease in the Young, Council on Cardiovascular and Stroke Nursing,
and Translational Biology, and Council on Lifestyle and Ca

European Heart Journal Advance Access published July 22, 2014

European Heart Journal
doi:10.1093/eurheartj/ehu274

REVIEW

Clinical update

Homozygous familial hypercholesterolaemia: nev insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society

Marina Cuchel*, Eric Bruckert, Henry N. Ginsberg, Frederick J. Raal, Raul D. Santos
Robert A. Hegele, Jan Albert Kuivenhoven, Børge G. Nordestgaard,
Olivier S. Descamps, Elisabeth Steinhagen-Thiessen, Anne Tybjærg-Hansen,
Gerald F. Watts, Maurizio Averna, Catherine Boileau, Jan Borén, Alberico L. Catapan
Joep C. Defesche, G. Kees Hovingh, Steve E. Humphries, Petri T. Kovanen, Luis Masan

European Heart Journal Advance Access published May 25, 2015

European Heart Journal
doi:10.1093/eurheartj/ehv157

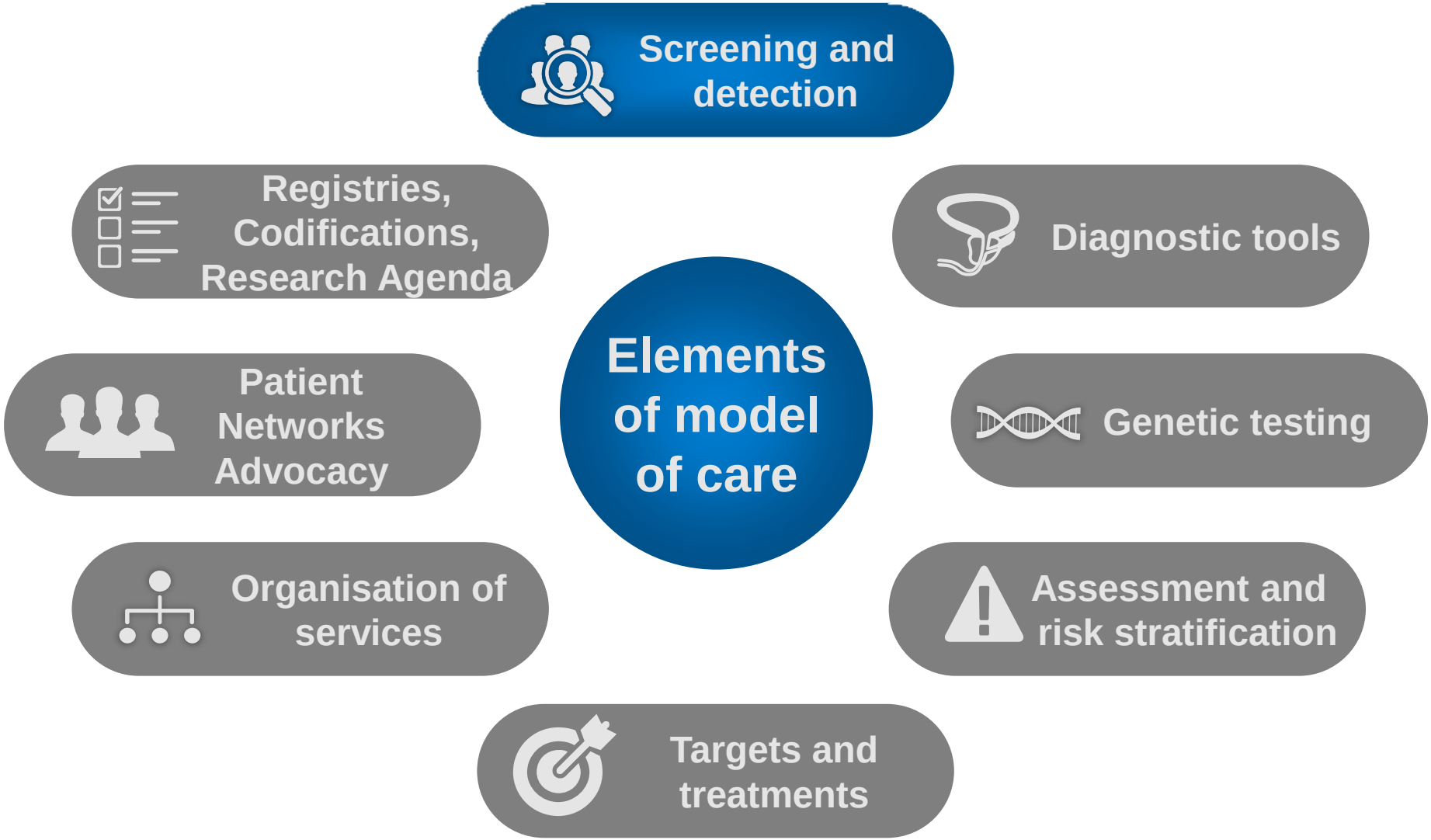
REV

Prevention

Familial hypercholesterolaemia in children anc adolescents: gaining decades of life by optimizi detection and treatment

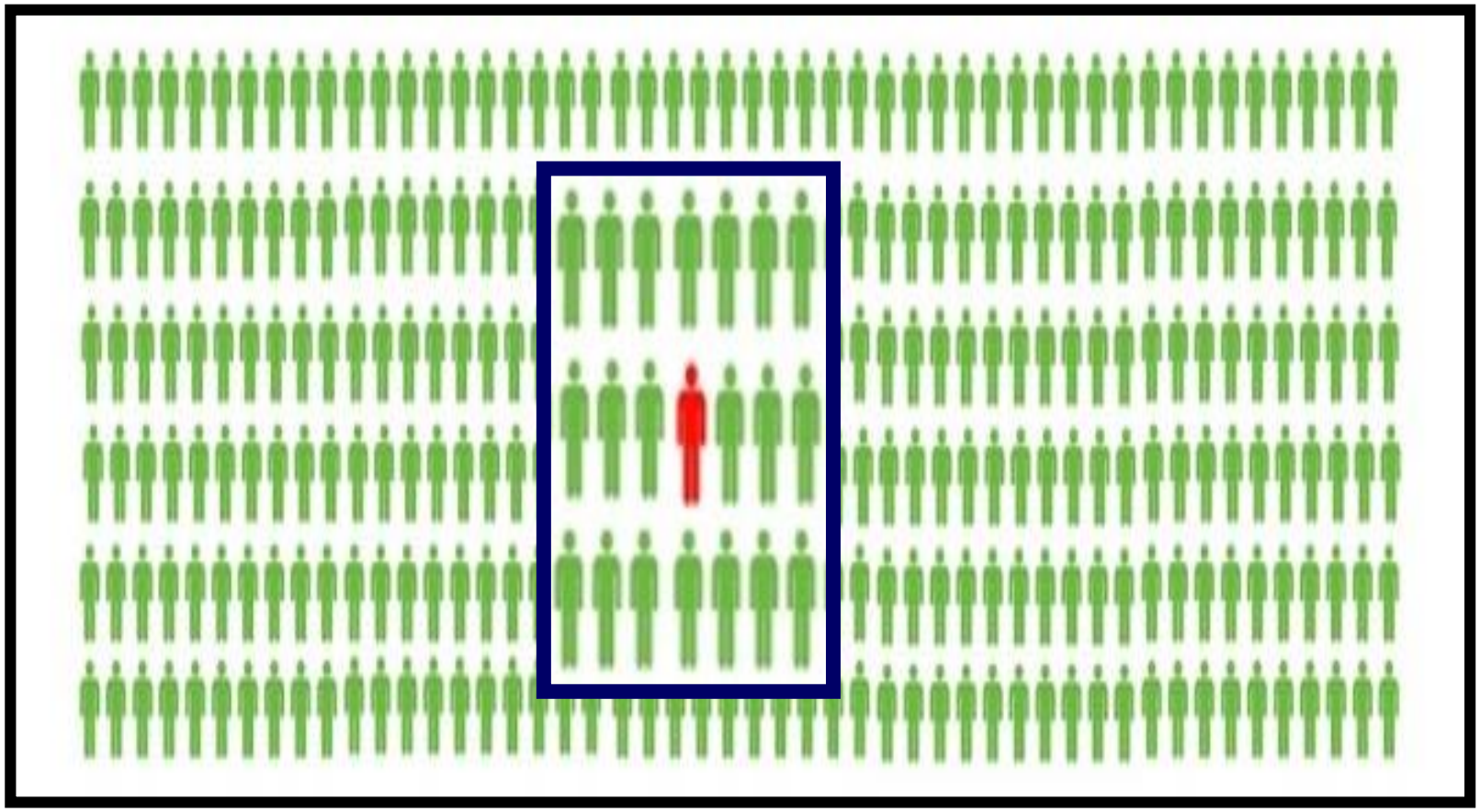
Albert Wiegman[1†*], Samuel S. Gidding[2†], Gerald F. Watts[3], M. John Chapman[4,
Henry N. Ginsberg[6,7], Marina Cuchel[8], Leiv Ose[9,10], Maurizio Averna[11],
Catherine Boileau[12,13,14], Jan Borén[15,16], Eric Bruckert[17], Alberico L. Catapano[1]

Anatomy of Care for FH



FH, familial hypercholesterolemia

At least 1 in 300 people have HzFH



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, Akioyamen LE BMJ Open 2017.

Detection Strategies

- Universal
- Systematic
- Opportunistic

Value of Cascade Testing for FH

- Earlier detection and initiation of preventive therapy
- Better adherence to therapy and reaching LDL-C goals
- Reduction in coronary events and suffering
- Proven cost-effective method of testing
- Reassurance for relatives who screen negative
- Supported by international guidelines and advocacy
- Classified as Tier 1 genomic application by CDCP

Knowles J W et al JAMA 2017;318:381-382. Umans-Eckenhausen et al Lancet 2001;357:165-168.
Perez de Isla L et al J Am Coll Cardiol. 2016;67:1278-1285. Gidding SS et al. Circulation 2015; 132 2167–2192.
National Collaborating Centre for Primary Care, Clinical Guideline 71: Familial Hypercholesterolaemia, London, UK, 2008.

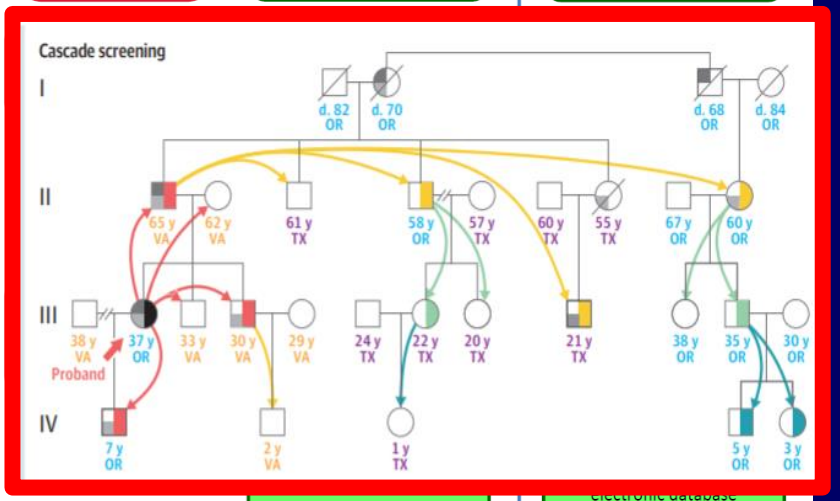
Dutch Lesson : how to do it

Cardiologists
Neurologists
Vascular surgeons
Internists
Ophthalmologists
Dermatologists
Pediatricians
General Practitioners
Clinical chemists
Chemical pathologists

Step 1: identify index cases

Raising awareness among population & health care professionals

Education population & health care professionals



Genetic Field workers

Step 4: risk notify; referrals

Internists
Pediatricians
General Practitioners
Specialist nurses

Start lipid lowering therapy early in life

Prevent cardiovascular disease and death

* If genetic testing is not available, such as in primary care or in developing countries, clinical diagnosis based on LDL-C levels can be used.

Louter L et al Athero Supp 2017; 30: 77-85.
Knowles J et al JAMA 2017;318:381-382.

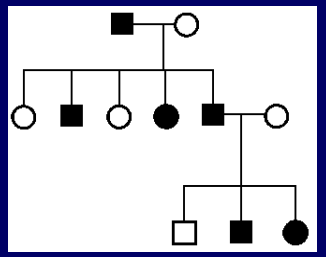
Problems with Cascade Testing

- Issues with privacy policies
- Lack of skills among providers
- Poor communication; family dynamics
- Geography, literacy, life insurance
- Model unsuited to healthcare systems
- Lack of re-imbursement
- Not suitable for population screening

Roberts MC et al Health Aff 2018 May;37:801-808. Sturm A et al Front Cardiovasc Med. 2016 ;3:11.
George R , Kovak K, Cox S J Genet Counsel 2015;24: 388-399. Knowles J et al JAMA 2017;318:381-382.
Morris JK et al Am J Med Genet A 2012 ;158A(1):78-84. Zimmerman et al J Community Genetics 2018 August

Universal Screening

Cascade Testing



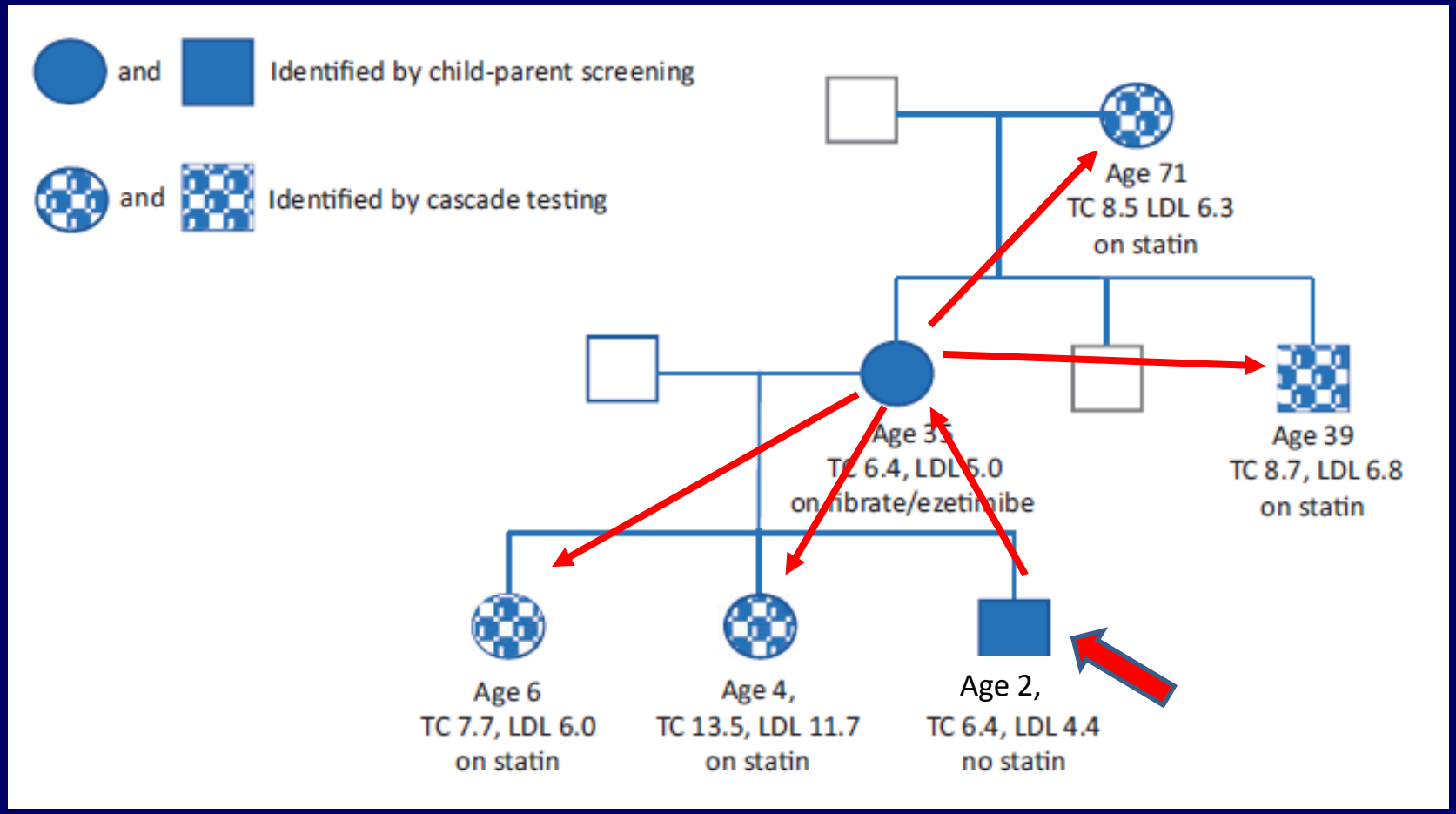
Opportunistic Testing

Integrated Detection Strategies

Type of Detection	Mode	Location
Universal Screening (children)	Phenotypic	Community Public Health
Systematic Cascade Testing (reverse/direct)	Phenotypic/ Genetic	Centralised Community
Opportunistic Testing (multiple)	Phenotypic	Primary Care Tertiary Care

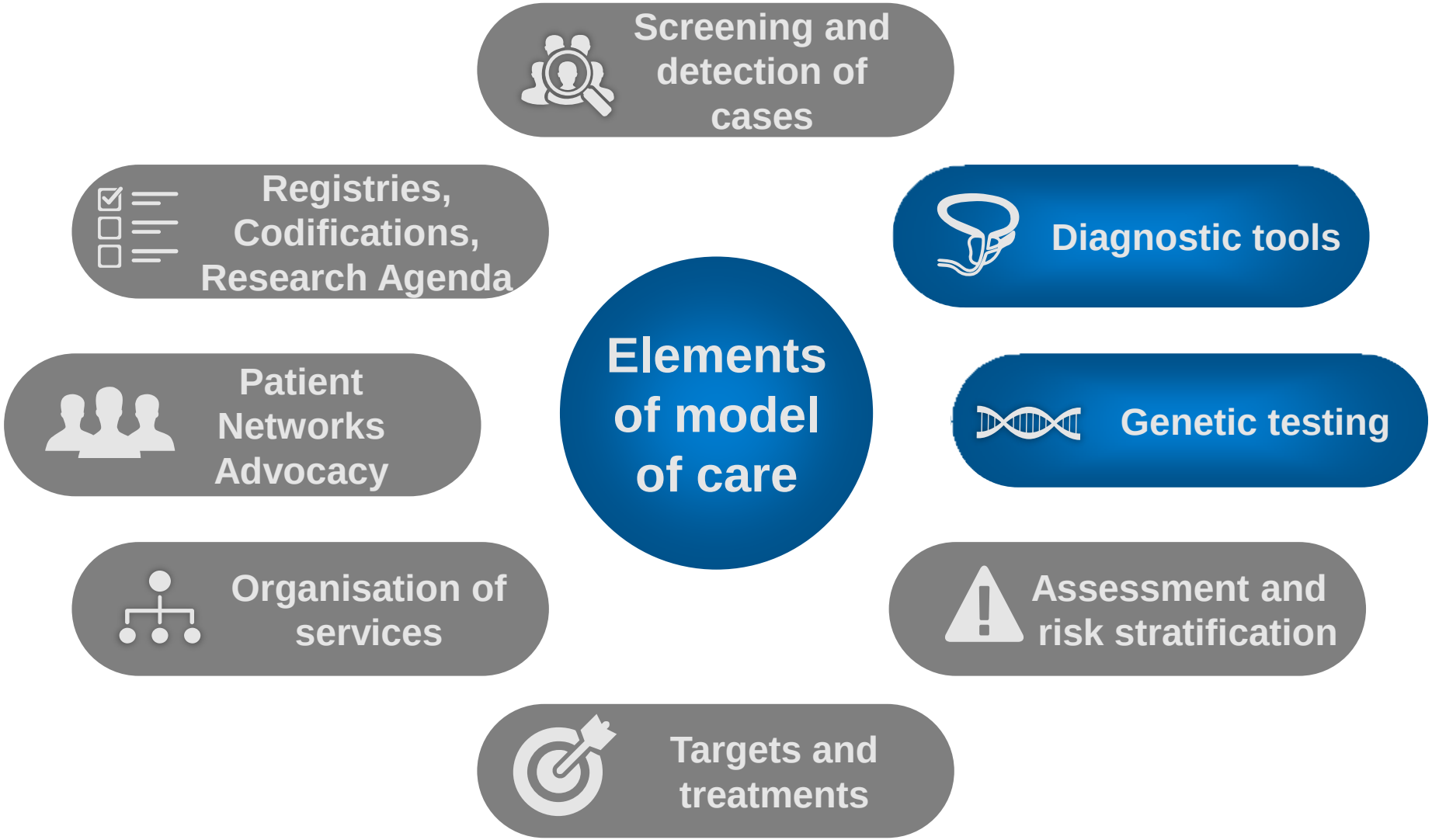
*Roberts MC et al Health Aff 2018 May;37:801-808. Sturm AC et al Front Cardiovasc Med. 2016 ;3:11. Watts GF et al Int J Cardiol 2014;171:309–25. Gidding SS et al. Circulation 2015; 132 2167–2192. Wiegman A et al Eur Heart J 2015; **36**, 2425–2437. Sturm AC et al J Am Coll Cardiol 2018;72:662-680.*

Integration of child-parent screening and cascade testing for FH (CPCS)

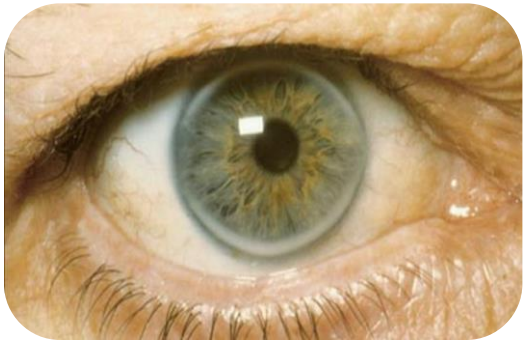


Wald D & Wald N J Med Screen 2018 (in press)
Wald D et al N Eng J Med 2016; 375: 1628–1637

Anatomy of Care for FH



Diagnosis of FH



Catapano et al Eur Heart J 2016; 37: 2999–3058

Table 21 Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolaemia[301]

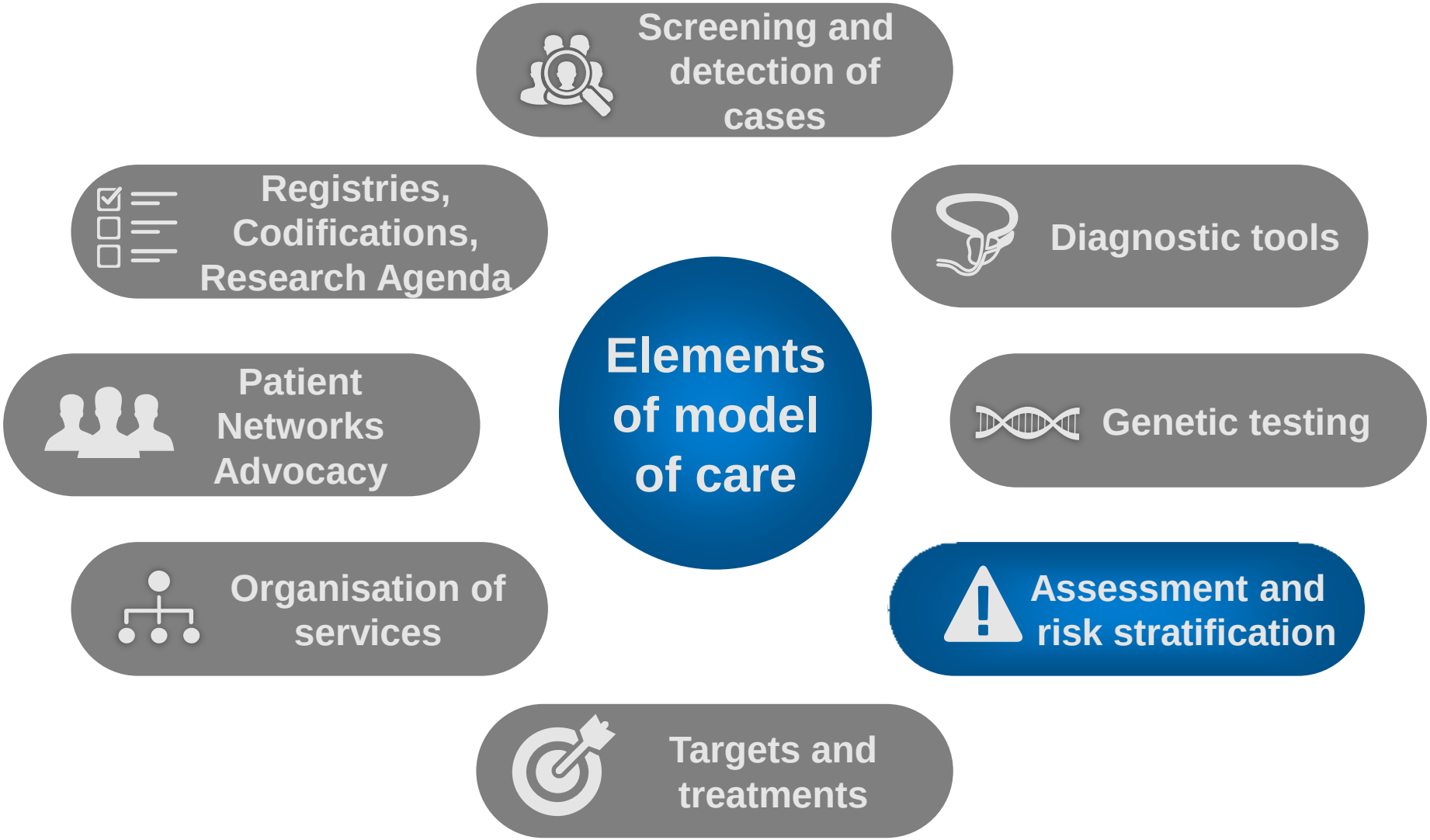
Criteria	Points
1) Family history	
First-degree relative with known premature (men: <55 years; women: <60 years) coronary or vascular disease, or	
First-degree relative with known LDL-C above the 95th percentile	1
First-degree relative with tendinous xanthomata and/or arcus cornealis, or	
children <18 years of age with LDL-C above the 95th percentile (see 9.1.2.3)	2
2) Clinical history	
Patient with premature (men: <55 years; women: <60 years) coronary artery disease	2
Patient with premature (men: <55 years; women: <60 years) cerebral or peripheral vascular disease	1
3) Physical examination	
Tendinous xanthomata	6
Arcus cornealis before age 45 years	4
4) LDL-C levels	
LDL-C ≥ 8.5 mmol/L (325 mg/dL)	8
LDL-C 6.5–8.4 mmol/L (251–325 mg/dL)	5
LDL-C 5.0–6.4 mmol/L (191–250 mg/dL)	3
LDL-C 4.0–4.9 mmol/L (155–190 mg/dL)	1
5) DNA analysis	
Functional mutation in the LDLR, apoB or PCSK9 gene	8
Choose only one score per group, the highest applicable Diagnosis (diagnosis is based on the total number of points obtained)	
A 'definite' FH diagnosis requires >8 points	
A 'probable' FH diagnosis requires 6–8 points	
A possible FH diagnosis requires 3–5 points	

Value of genetic testing in FH

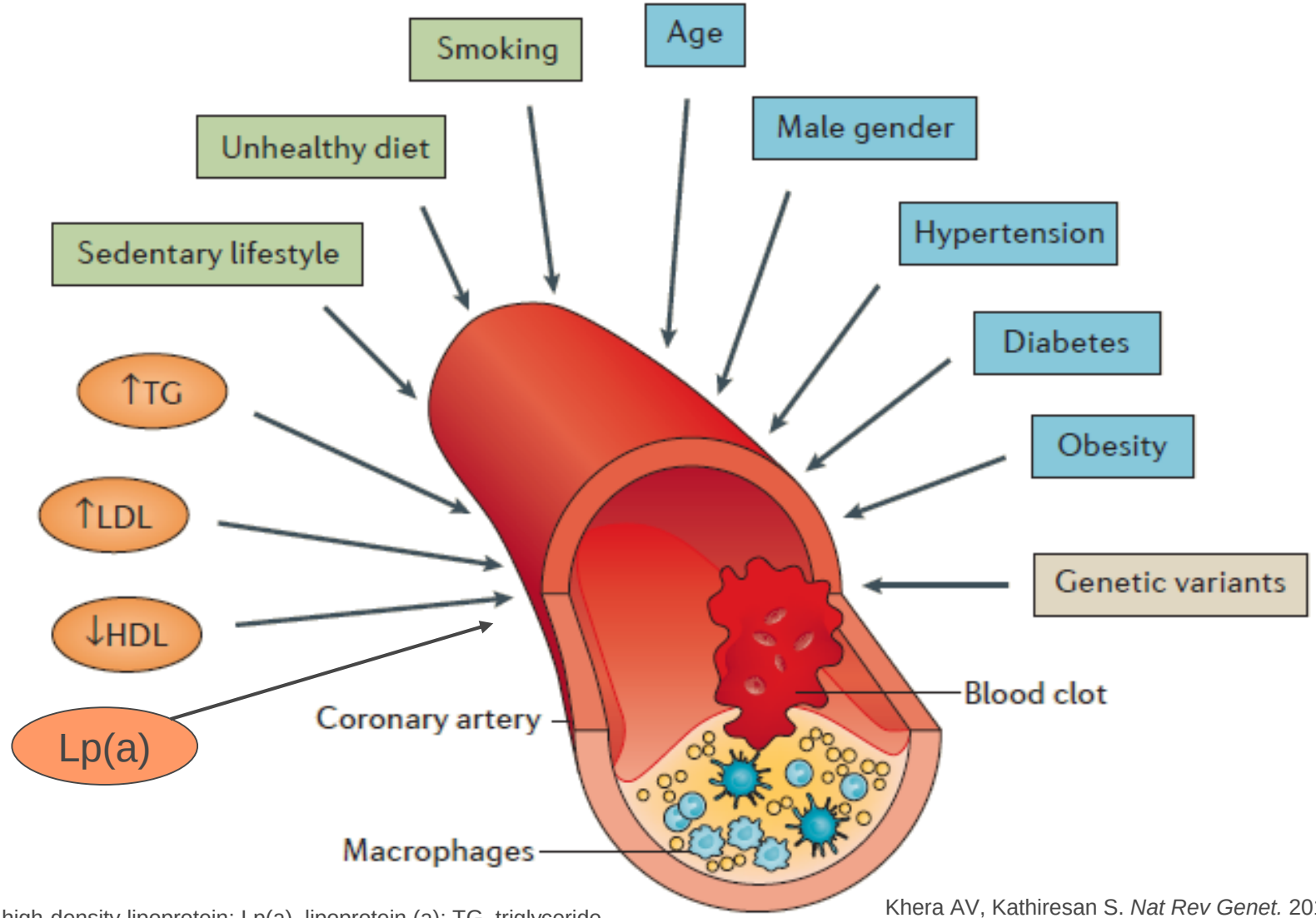
- **Increases precision of diagnosis**
- **Improves risk prediction**
- **Facilitates cascade testing**
- **Improves genetic counselling**
- **Enables good therapeutic choices**
- **Improves adherence to therapies**

Khera AV *et al. J Am Coll Cardiol* 2016;67:2578–89. . .
Defesche JC *et al. Nat Rev Dis Primers* 2017;3:17093.
Sturm AC et al *J Am Coll Cardiol* 2018;72:662-680

Anatomy of Care for FH



Development of atherosclerosis in FH is dependent of many risk modifiers

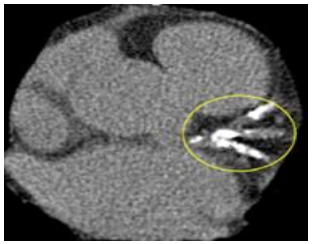
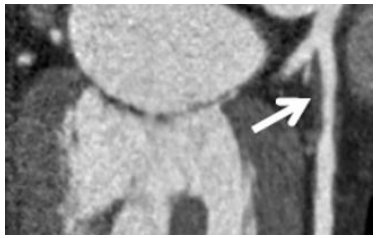
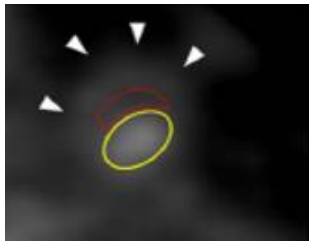
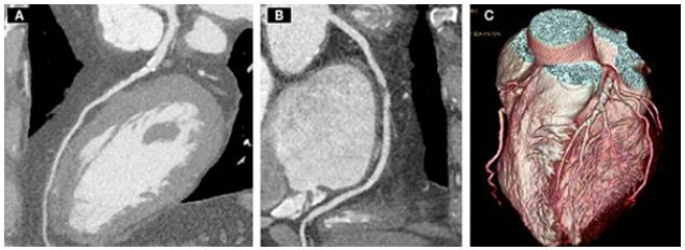


HDL, high-density lipoprotein; Lp(a), lipoprotein (a); TG, triglyceride

Khera AV, Kathiresan S. *Nat Rev Genet.* 2017;18:331-344
Perez de Isla L *et al Circulation* 2017;135:2133–44.

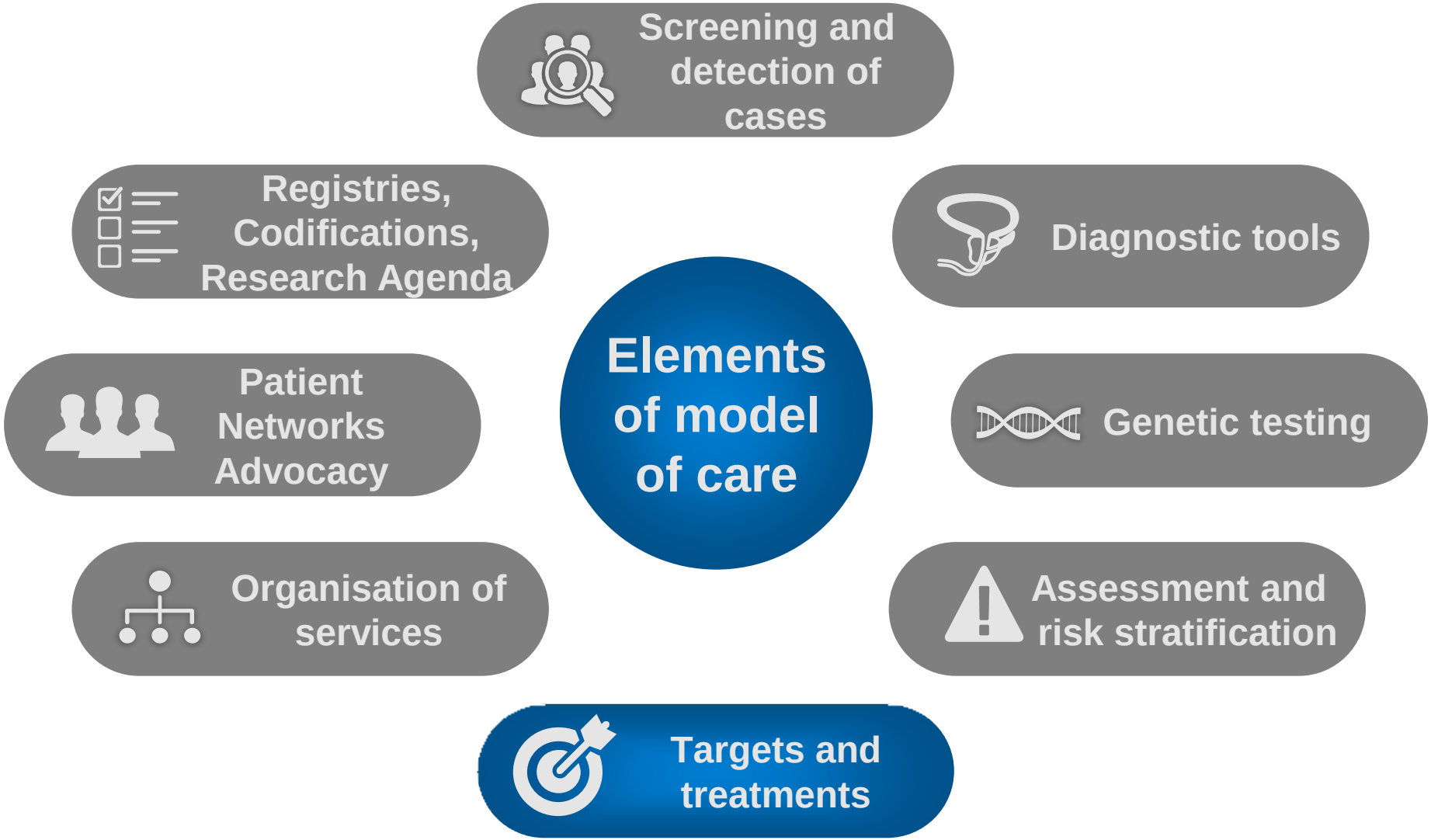
Value of Cardiac CT Scan in FH

- **Integrates cholesterol-life years**
- **Guides intensity of therapy**
- **Increases adherence to therapy**
- **Triages further investigation**

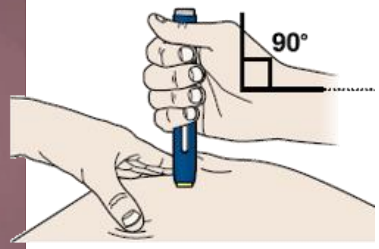





Miname et al J Am Coll Cardiol Img 2018
Sijbrands E et al Curr Opin Lipidol 2015

Anatomy of Care for FH



Four Principles for LDL Lowering in FH



Treatment options

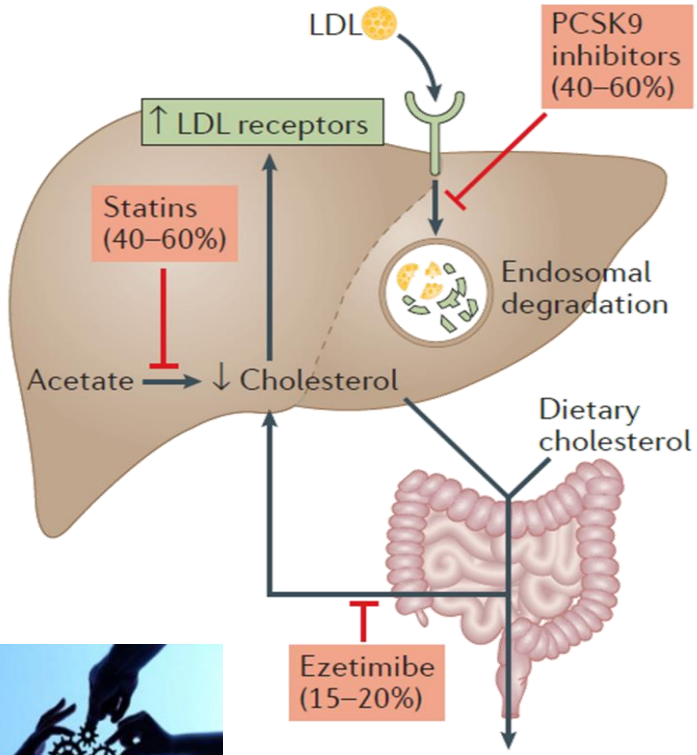
- **Heart healthy lifestyle, nutraceuticals**
- **Established drugs**
  - Statin, ezetimibe, resin, niacin
- **New drugs**
  - PCSK9 mAb, ApoB antisense, MTP inhibition
- **Advanced and radical therapies**
  - Lipoprotein apheresis, liver transplant

ApoB, apolipoprotein B; ASO, antisense oligonucleotides; mAb, monoclonal antibody; MTPi, microsomal triglyceride transfer protein inhibitor, PCSK9, proprotein convertase subtilisin/kexin type 9

Page MM & Watts GF. *Diabetes Obes Metab* 2017;20:270–82.

Multiple recommendations on use of PCSK9 monoclonal antibodies

- **American Heart Association/American College of Cardiology**
  - Grundy SM et al *Circulation 2018 Nov 3rd*
- **American Heart Association**
  - Gidding SS *et al. Circulation* 2015;132:167–92.
- **American College of Cardiology**
  - Lloyd-Jones DM *et al. J Am Coll Cardiol* 2017;70:1785–822.
- **International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel**
  - Santos RD *et al. Lancet Diabetes Endocrinol* 2016;4:850–61.
- **European Society of Cardiology (ESC) / European Atherosclerosis Society (EAS) Task Force**
  - Landmesser U *et al. Eur Heart J 2018;39:1131-1143*
- **European Society of Cardiology**
  - Catapano AL *et al. Eur Heart J* 2016;37:2999–3058.
- **American Association of Clinical Endocrinologists / American College of Endocrinology**
  - Jellinger PS *et al Endocr Pract* 2017;23(Suppl 2):1–87.
- **National Lipid Association**
  - Orringer CE *et al. Clin Lipidol* 2017;11:880–90.



EAS/ESC Taskforce on PCSK9 mAbs

Patients with clinically diagnosed ASCVD (CAD, symptomatic PAD, ischaemic stroke) on maximally tolerated statin therapy

± Ezetemibe

LDL-C >**2.6** mmol/L (>**100** mg/dL) and
with additional indices of risk severity

Including

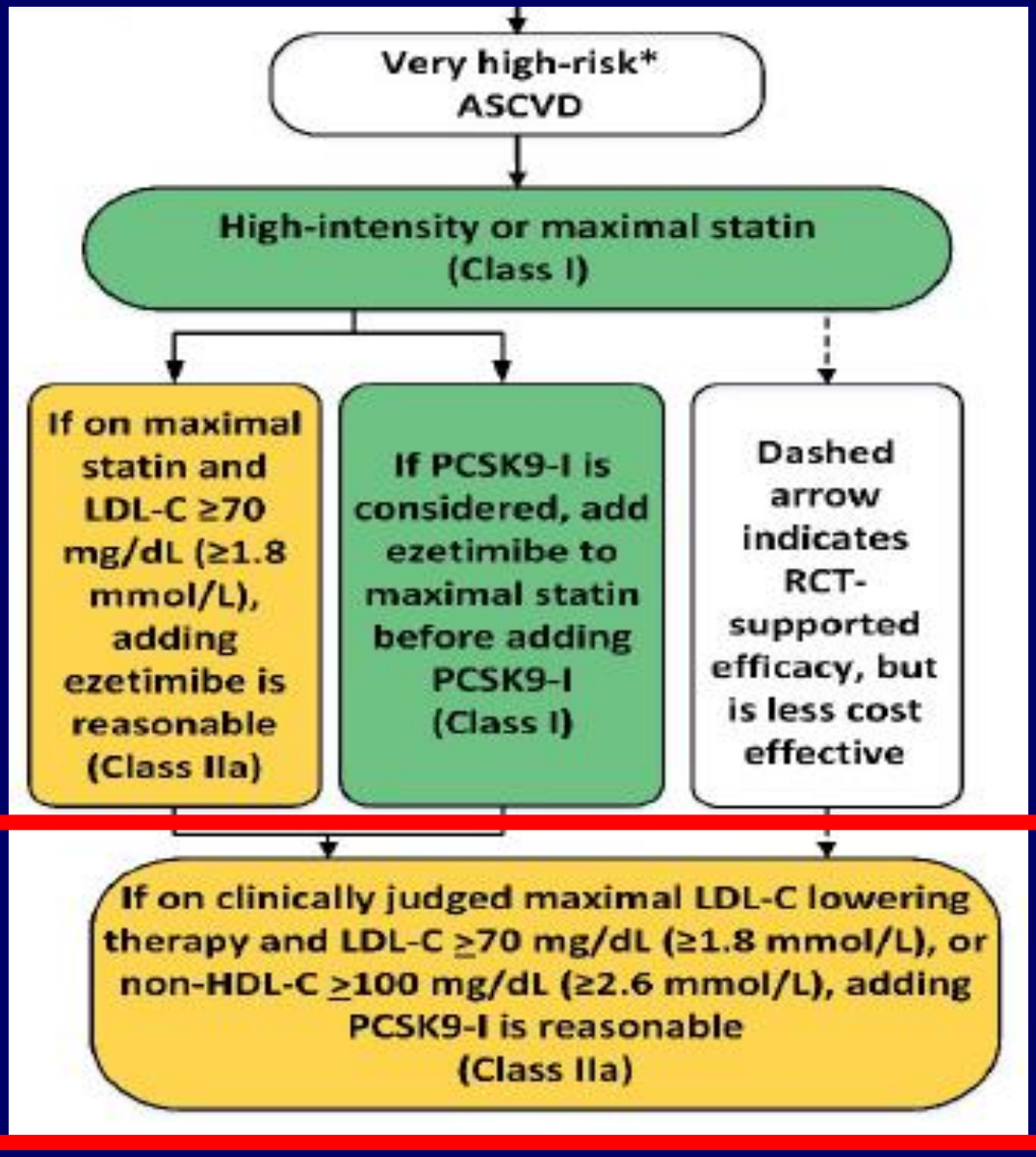
- **Familial hypercholesterolemia**
- **Diabetes mellitus** with target organ damage (eg proteinuria) or with a major risk factor such as marked hypertension
- **Severe and/or extensive ASCV (eg severe polyvascular disease, extensive coronary disease**
- Rapid progression of ASCVD ie repeated ACS, unplanned coronary revascularizations or ischaemic strokes within 5 years of index event

LDL-C >**3.6** mmol/L (>**140** mg/dL)

Should consider a PCSK9 mAb

Landmesser U et al Eur Heart J 2018;39:1131-1143

AHA/ACC Cholesterol Guidelines



Grundy SM et al Circulation 2018 Nov 10 th

EAS/ESC Taskforce on PCSK9 mAbs

Patients with FH without clinically diagnosed ASCVD
on maximally tolerated statins plus ezetimibe therapy

Check for additional indices of risk severity

- Diabetes mellitus with target organ damage (eg proteinuria), or with a major risk factor (eg marked hypertension)
- Lp(a) >50 mg/dL
- Major risk factors: smoking, marked hypertension
- >40 years of age without treatment
- Premature ASCVD (<55 years in males and <60 years in females) in first-degree relatives
- Imaging indicators

Additional indices of risk severity
LDL-C >**3.6** mmol/L (>**140** mg/dL)

No additional indices of risk severity
LDL-C >**4.5** mmol/L (>**180** mg/dL)

May consider a PCSK9 mAb

Landmesser U et al Eur Heart J 2018;39:1131-1143

4.2. Severe Hypercholesterolemia (LDL-C ≥190 mg/dL [≥4.9 mmol/L])

COR	LOE	Recommendations
IIb	B-R	4. In patients 30 to 75 years of age with heterozygous FH and with an LDL-C level of 100 mg/dL (≥2.6 mmol/L) or higher while taking maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered (S4.2-9, S4.2-13–S4.2-15).
Value Statement: Uncertain Value (B-NR)		6. Among patients with FH without evidence of clinical ASCVD taking maximally tolerated statin and ezetimibe therapy, PCSK9 inhibitors provide uncertain value at mid-2018 U.S. list prices.

AMERICAN COLLEGE of CARDIOLOGY

Grundy SM et al Circulation 2018 Nov 10 th

American Heart Association.

The NEW ENGLAND JOURNAL of MEDICINE

DOI: 10.1056/NEJMoa1812792

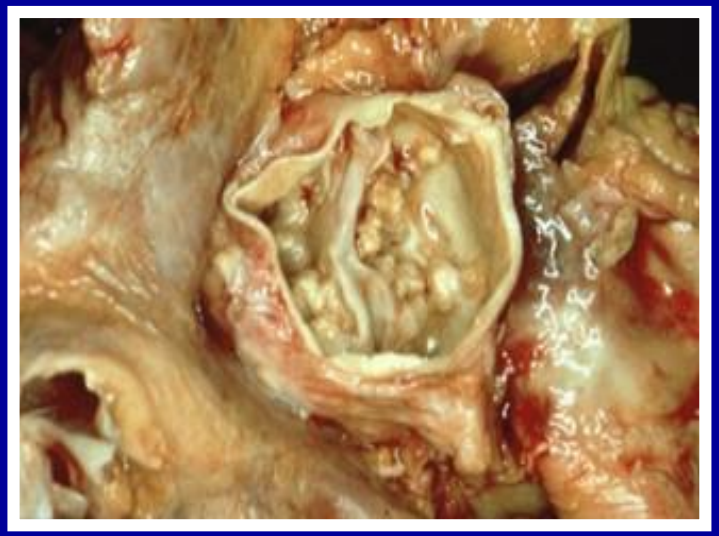
ORIGINAL ARTICLE

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D., Eliot A. Brinton, M.D., Terry A. Jacobson, M.D., Steven B. Ketchum, Ph.D., Ralph T. Doyle, Jr., B.A., Rebecca A. Juliano, Ph.D., Lixia Jiao, Ph.D., Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and Christie M. Ballantyne, M.D., for the REDUCE-IT Investigators*

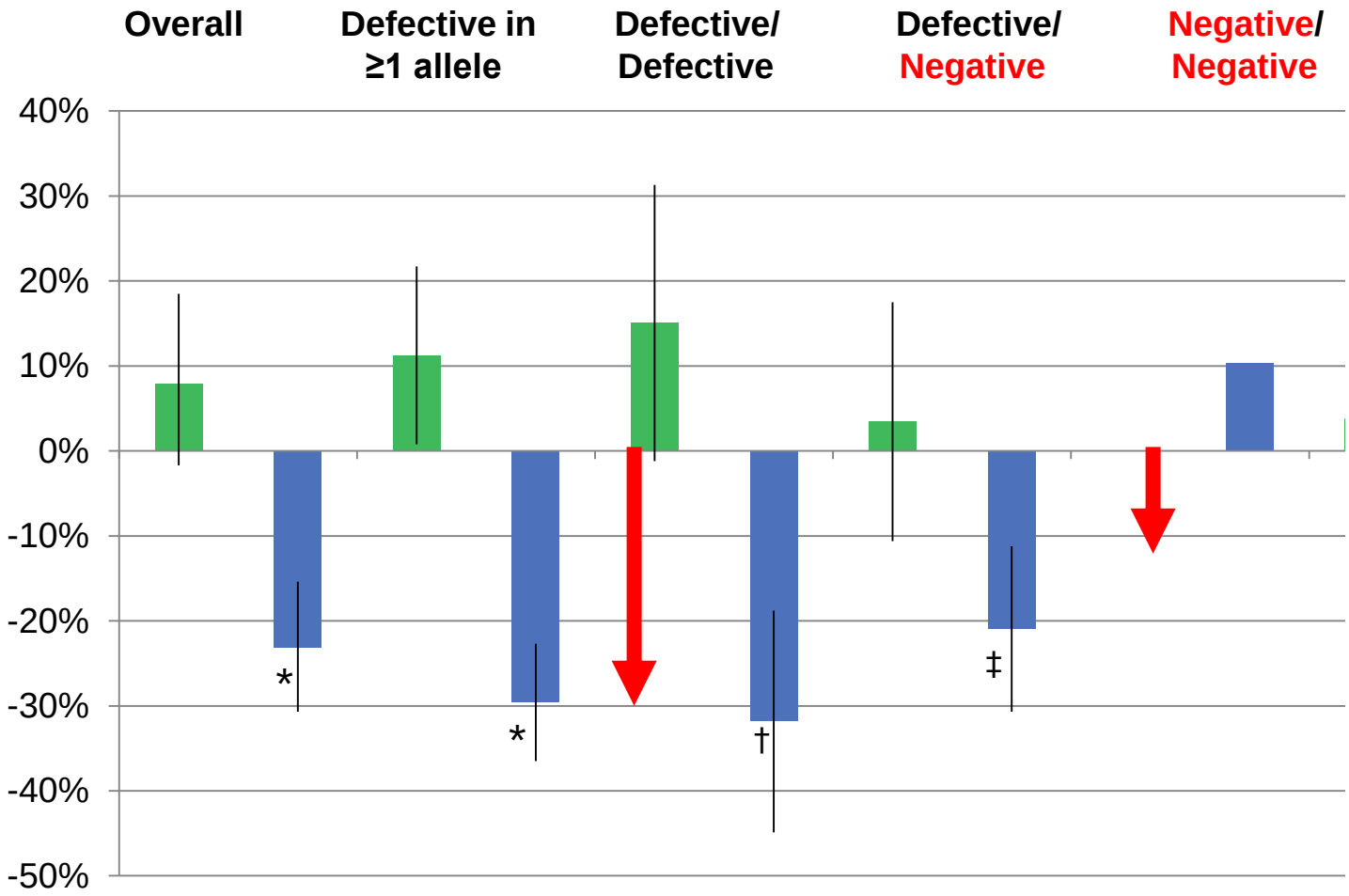
Prespecified Hierarchical Testing Results	icosapent ethyl	placebo	
Composite primary endpoint	17.2%	22.0%	25% reduction HR=0.75 P<0.001
Composite secondary endpoint	11.2%	14.8%	HR=0.74 P<0.001

Severe homozygous FH



Cuchel et al EAS Eur Heart J 2014

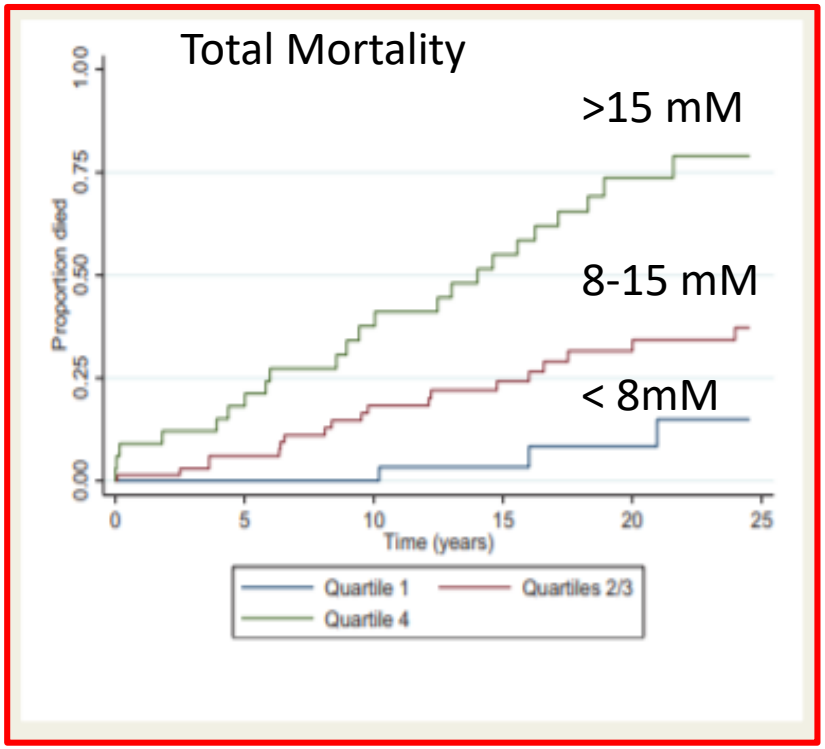
Evolocumab: change in LDL-C in hoFH patients by LDL receptor mutation type

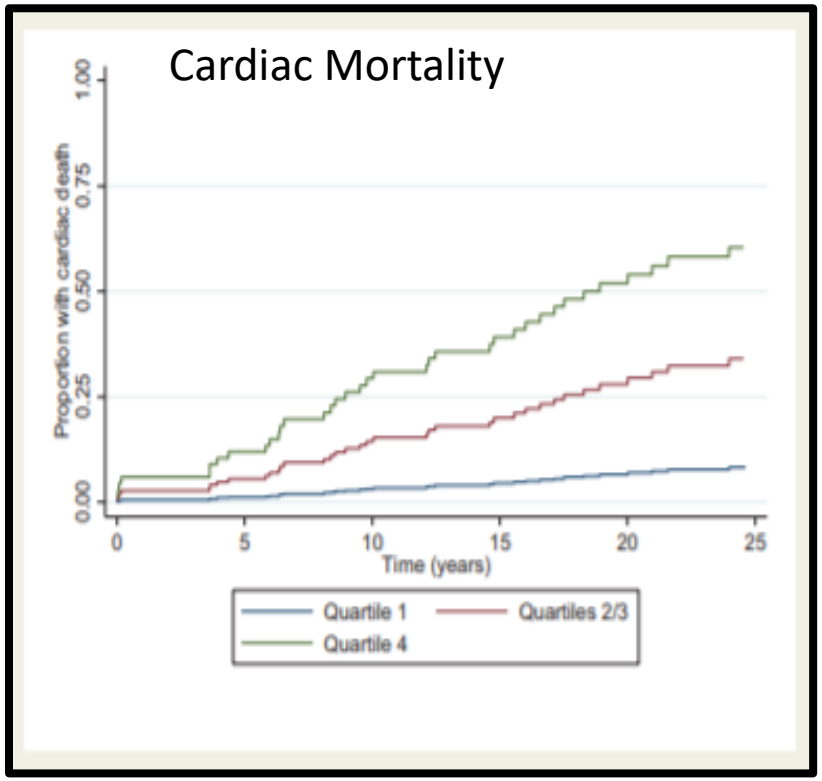


*Adjusted P<0.0001; †P<0.001; ‡P<0.05.

Raal FJ et al. Lancet 2014

Survival Analyses with Apheresis by on Treatment Cholesterol in HoFH Patients





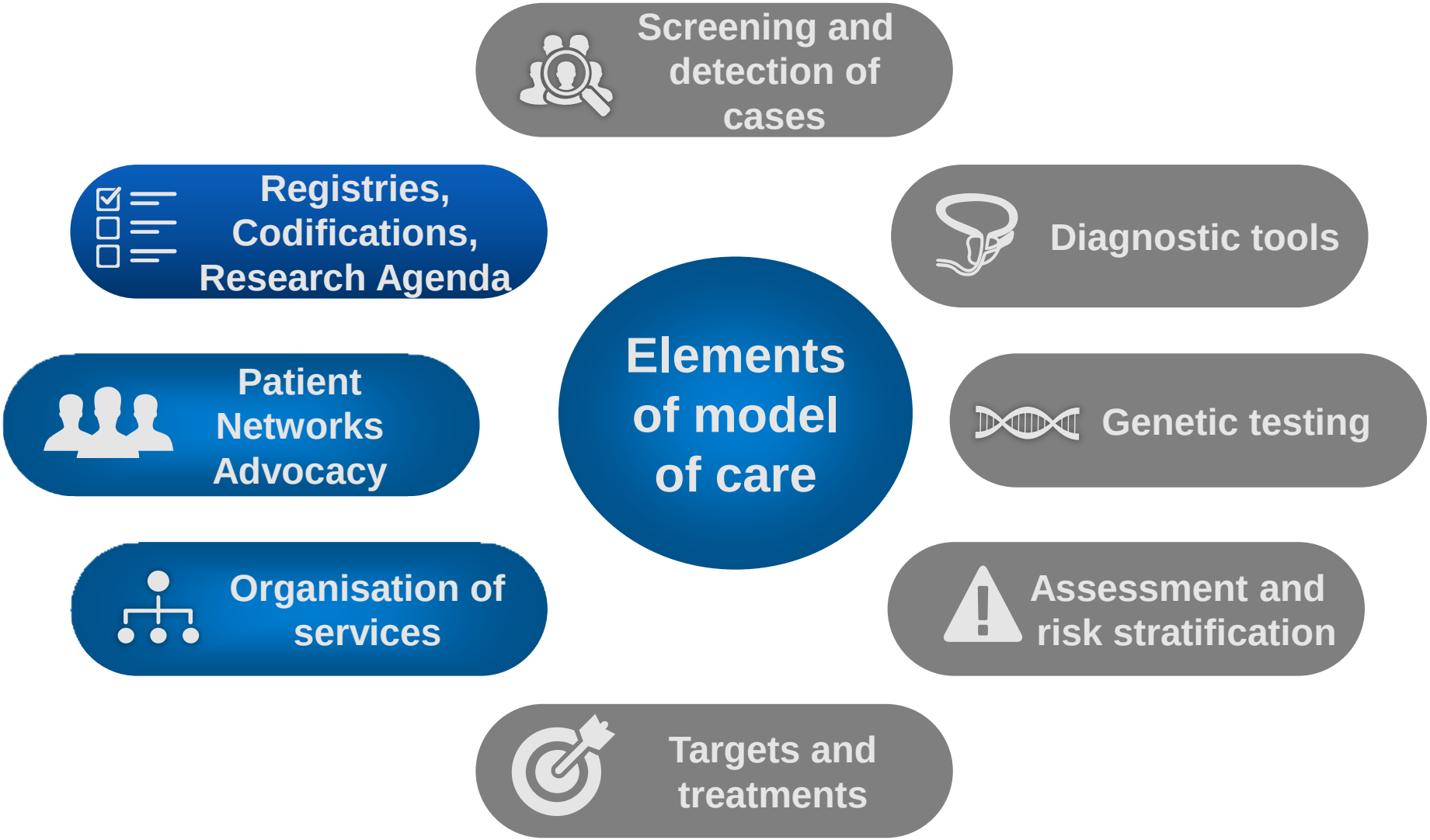
Thompson et al Eur Heart J 2018 ;39(14):1162-1168

New Therapies for HoFH

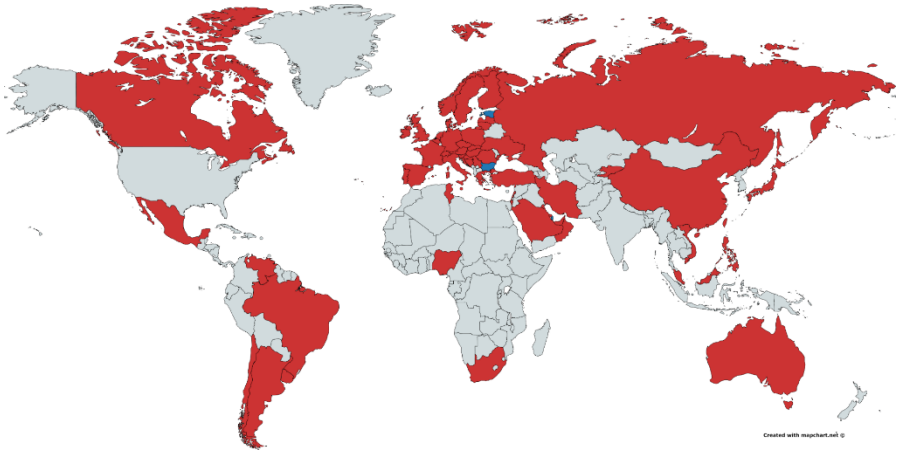
- **Evinacumab***
- **Gemcabene**
- **Gene therapy**

** Gaudet D et al N Engl J Med 2017; 377: 296-297*

Anatomy of Care for FH



FH Registries

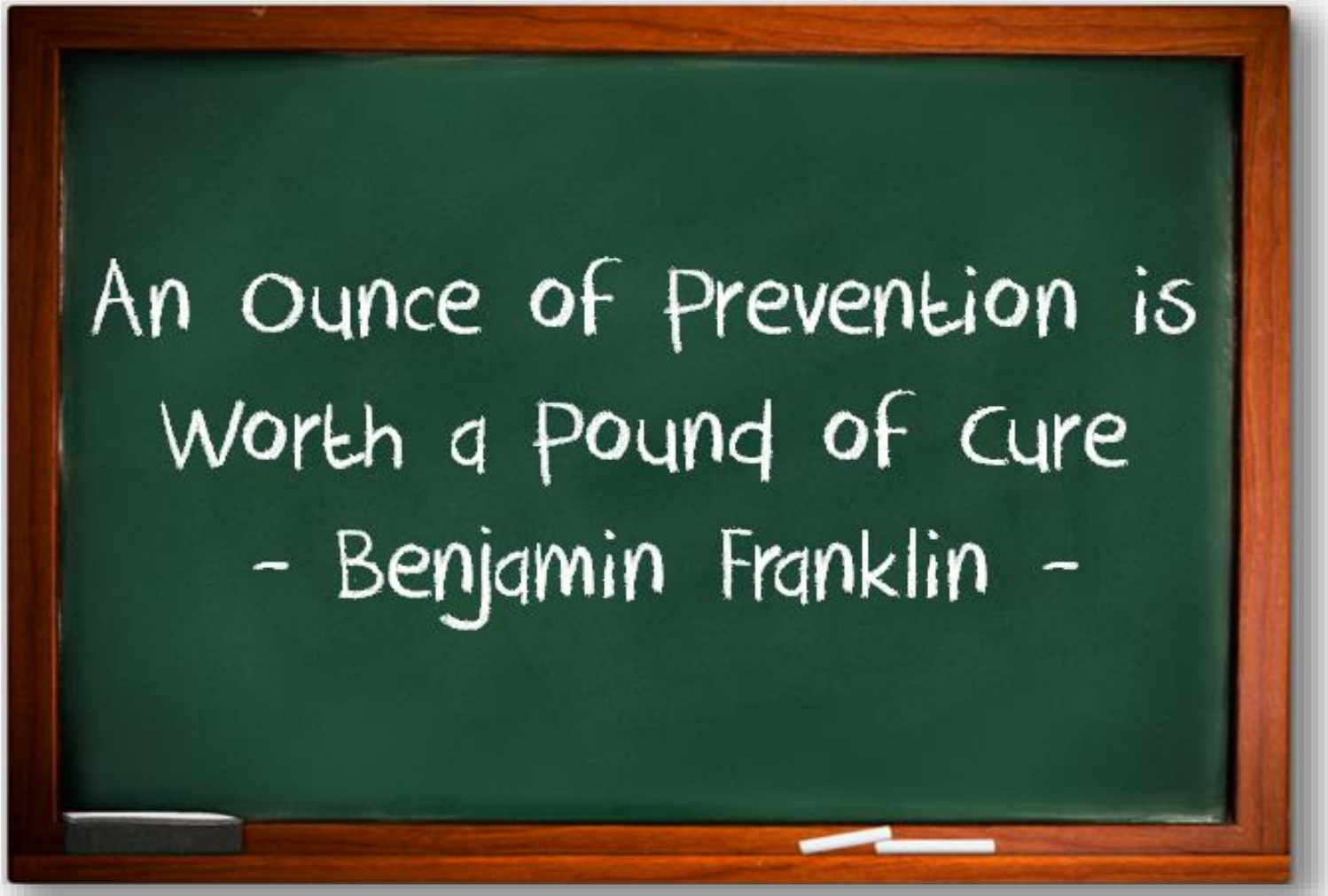


MED-PED, SB-UK
Netherlands, Norway
SAFE-HEART……
USFHF, FHSC.

Take 7 Messages Home

1. High prevalence of FH implies a public health issue
2. Screening methods need co-ordination; cascade is limited
3. Genetic testing is valuable; consider costs and preferences
4. Risk stratification: new risk equations and imaging
5. Start statins early; any LDL reduction is important in HoFH
6. PCSK9 inhibition for higher risk FH; new agents for HoFH
7. Integration, codification and registration of care is essential

Final Words……


An Ounce of Prevention is
Worth a Pound of Cure
- Benjamin Franklin -