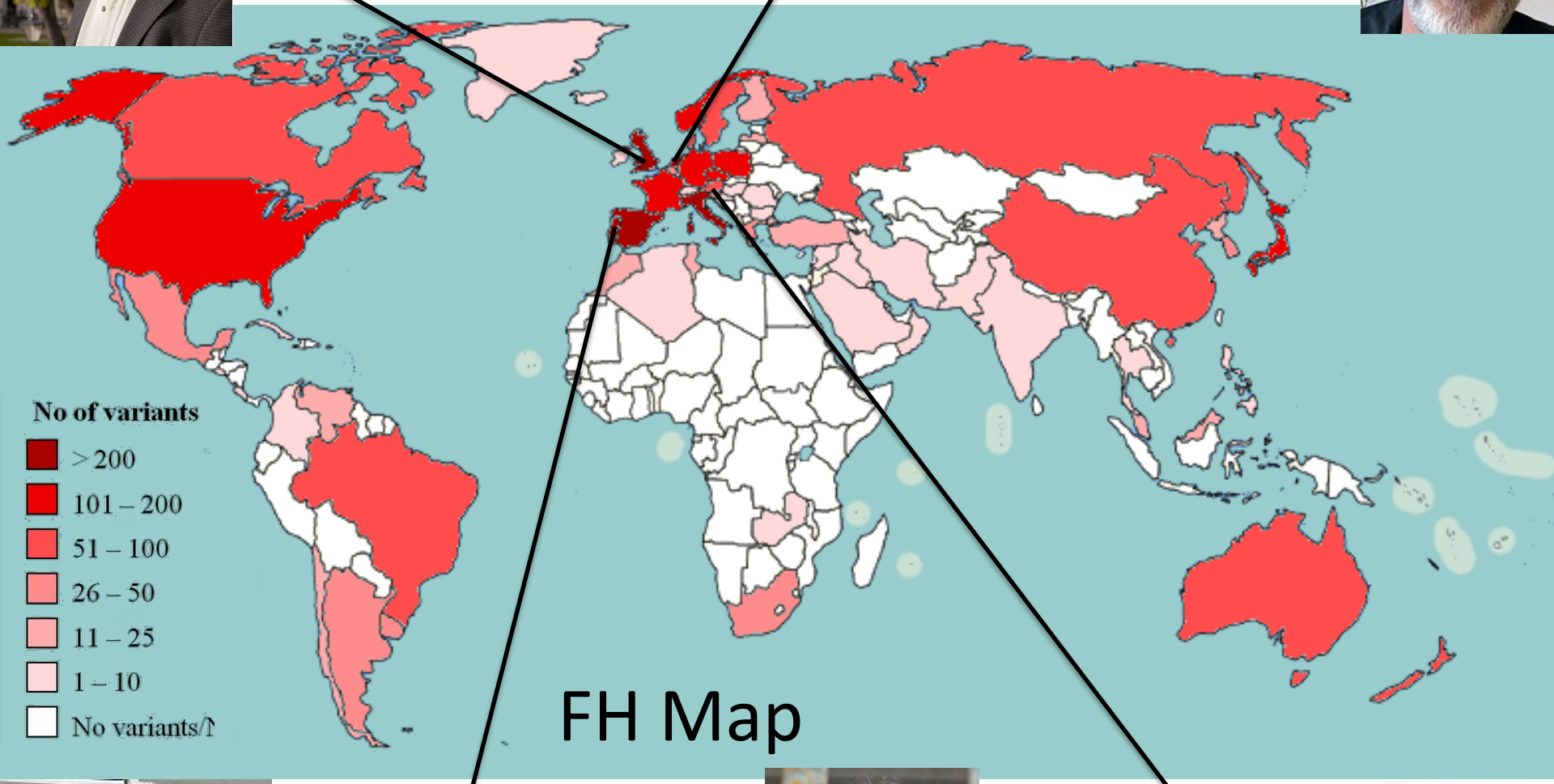
FH Europe

UK - Steve Humphries

Market access and Precision medicine for FH

Netherlands - Eric Sijbrands

Clinical Studies and Health system implementation



FH Map

Portugal

Mafalda Bourbon

Mechanism of disease and research effort

João Lavinha

E.L.S.I

Austria –

Gaby Hanauer

Patient benefit

Translational medicine in Familial Hypercholesterolemia – from phenotype, to genotype to treatment

Mechanism of disease and research effort

Mafalda Bourbon, PhD
Head of R&D Unit and Head of Cardiovascular Research Group,
Department of Health Promotion, INSA
Invited Professor, BioISI, FCUL

REPÚBLICA PORTUGUESA
SAÚDE

Instituto_Nacional de Saúde
Doutor Ricardo Jorge

BioISI
Biosystems and Integrative Sciences Institute

Familial hypercholesterolemia (FH)

FH is the most common monogenic lipid disorder

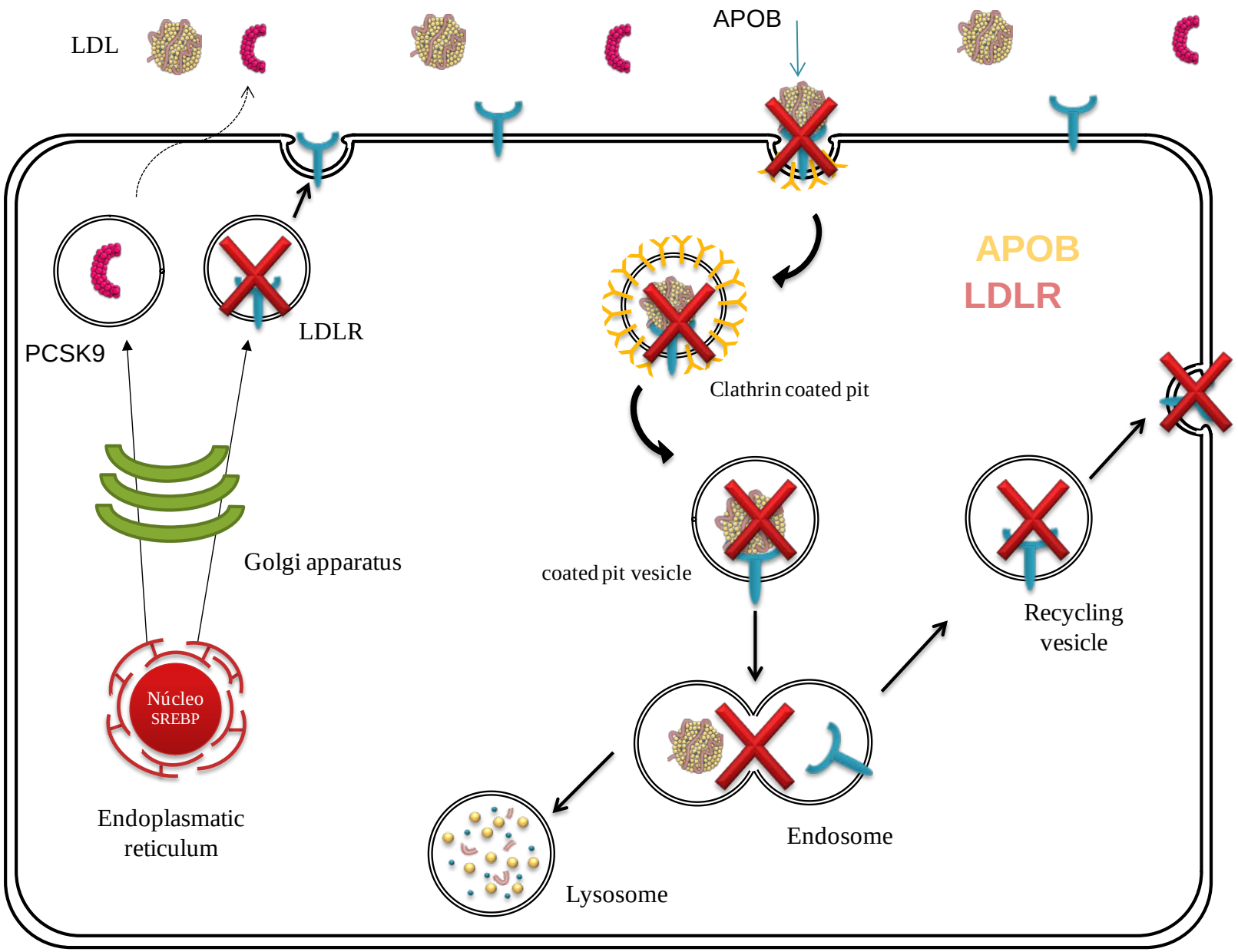
- Autosomal dominant disorder
- Heterozygote prevalence: 1/250 − 1/500
- Homozygous is more rare: 1/300 000 − 1/1,000 000
- >90% cases are due to LDLR mutations; 5-10% *APOB*; 1-3% *PCSK9*
- Patients present very high LDL values from birth
- Under-diagnosed and under-treated although there are established clinical criteria

Due to long life exposure to high LDL cholesterol levels patients develop

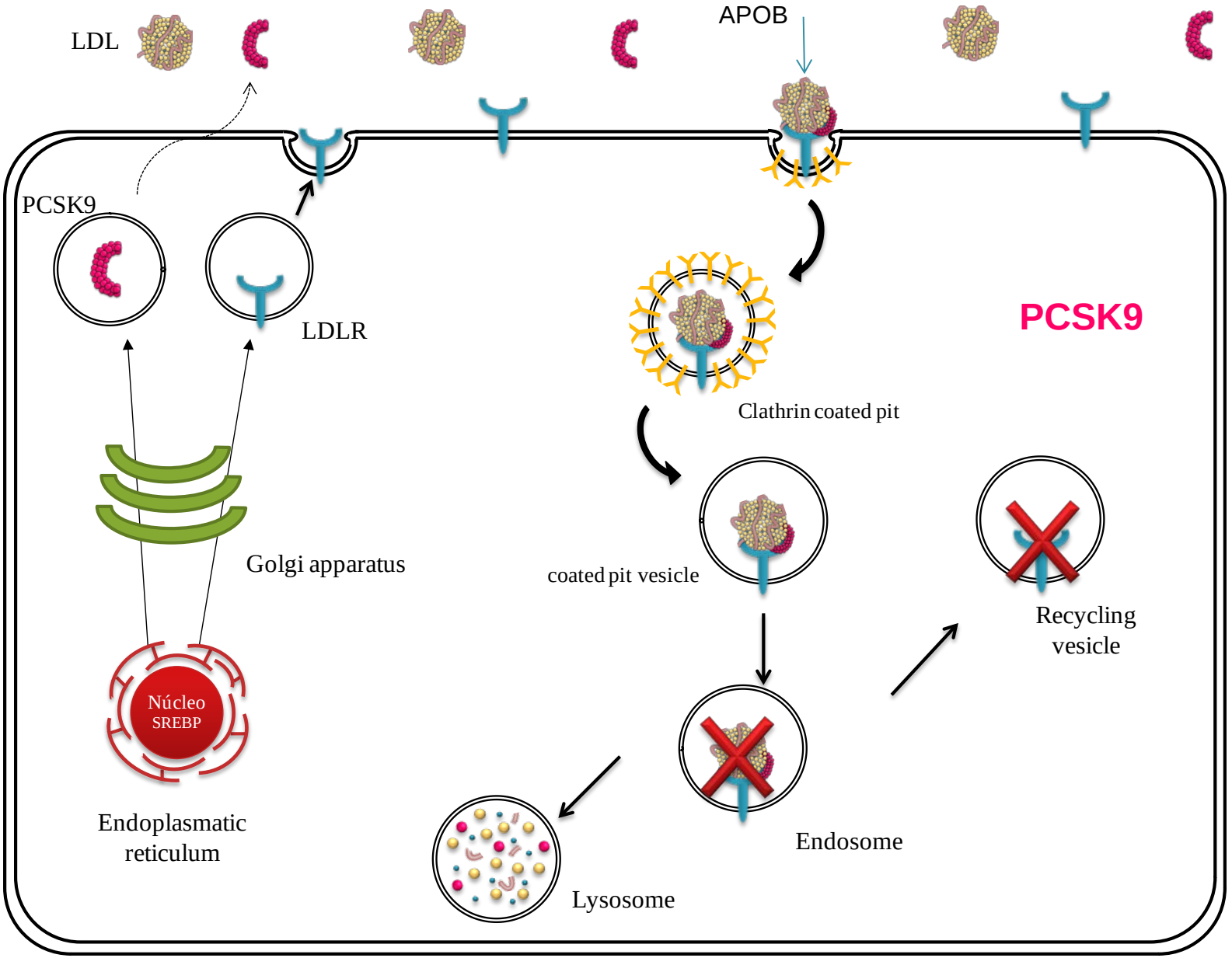
premature coronary heart disease

It is possible to have an accurate diagnosis and treatment that will reduce cardiovascular risk

LDLR cycle



LDLR cycle



Genetics of Familial Hypercholesterolemia

Now - More than 2800 variants associated to FH in ClinVar

	LDLR	*APOB*	*PCSK9*	Total
All variants submitted to ClinVar	5174	1003	474	6651
Variants detected in FH patients	4973	580	355	5908
Unique variants detected in FH patients	2314	353	216	2883

Iacocca & Chora et al, 2018

Clinical Genome (ClinGen) Resource

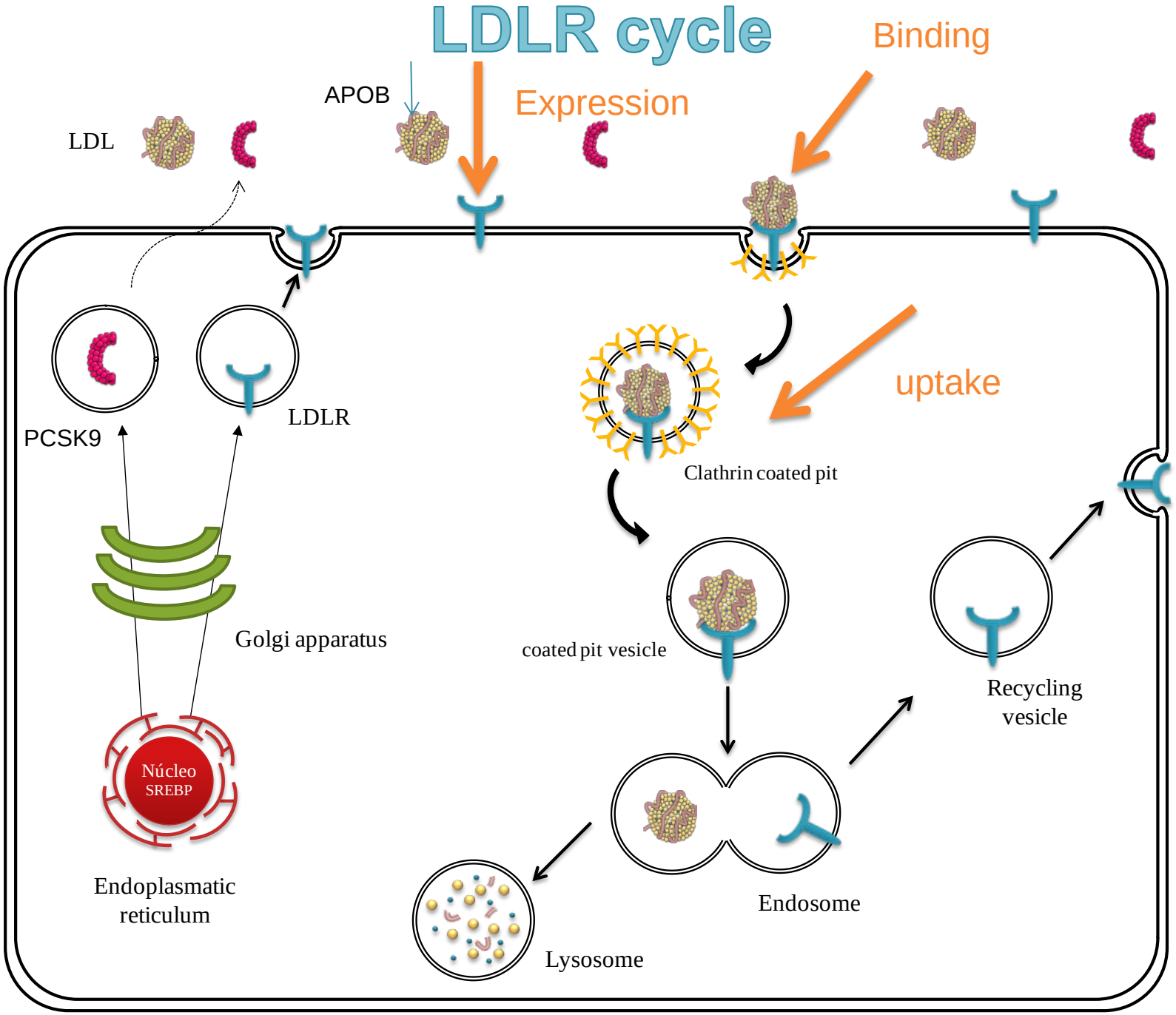
An NIH funded consortium in collaboration with ClinVar
coordinated by Stanford, Harvard and North Carolina Universities

ClinGen is dedicated to building an authoritative central resource that defines the clinical relevance of genes and variants for use in precision medicine and research

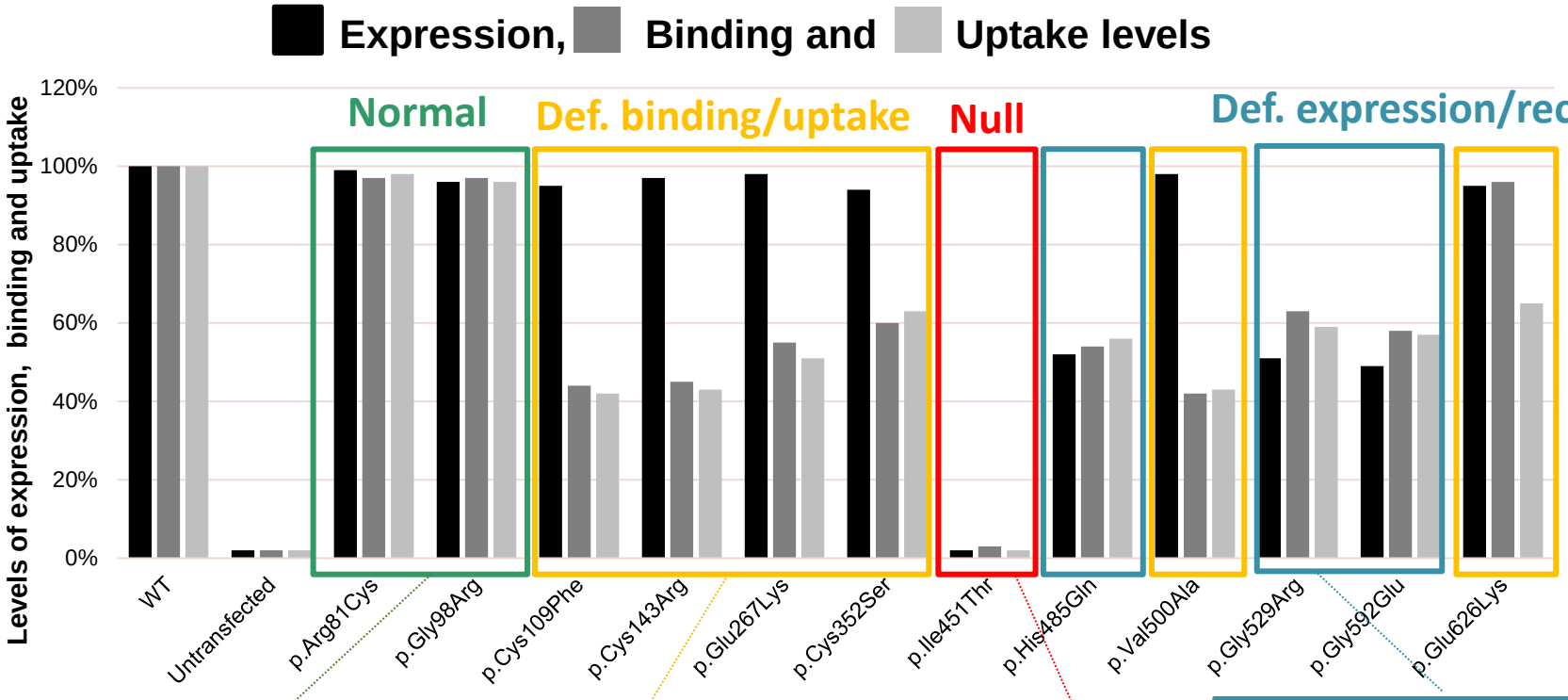
FH variant curation expert panel

(chairs: Mafalda Bourbon, INSA, Portugal; Josh Knowles, Stanford, USA)

- **Promote FH associated variants submission to ClinVar** ✔
- **Develop an FH specific algorithm** on going
- **Curate all FH variants in ClinVar** 2019



From phenotype to functional genotype to treatment – personalized medicine



Phenotype due to others genetic/ environmental causes; treat accordingly

Protein retain some activity - milder to severe phenotype;
Statin + inhibitor of intestinal cholesterol absorption

LDLR recycling defective - milder phenotype;
statin

Residual or no protein - severe phenotype;
Potent statin + inhibitor of intestinal cholesterol absorption + iPCSK9

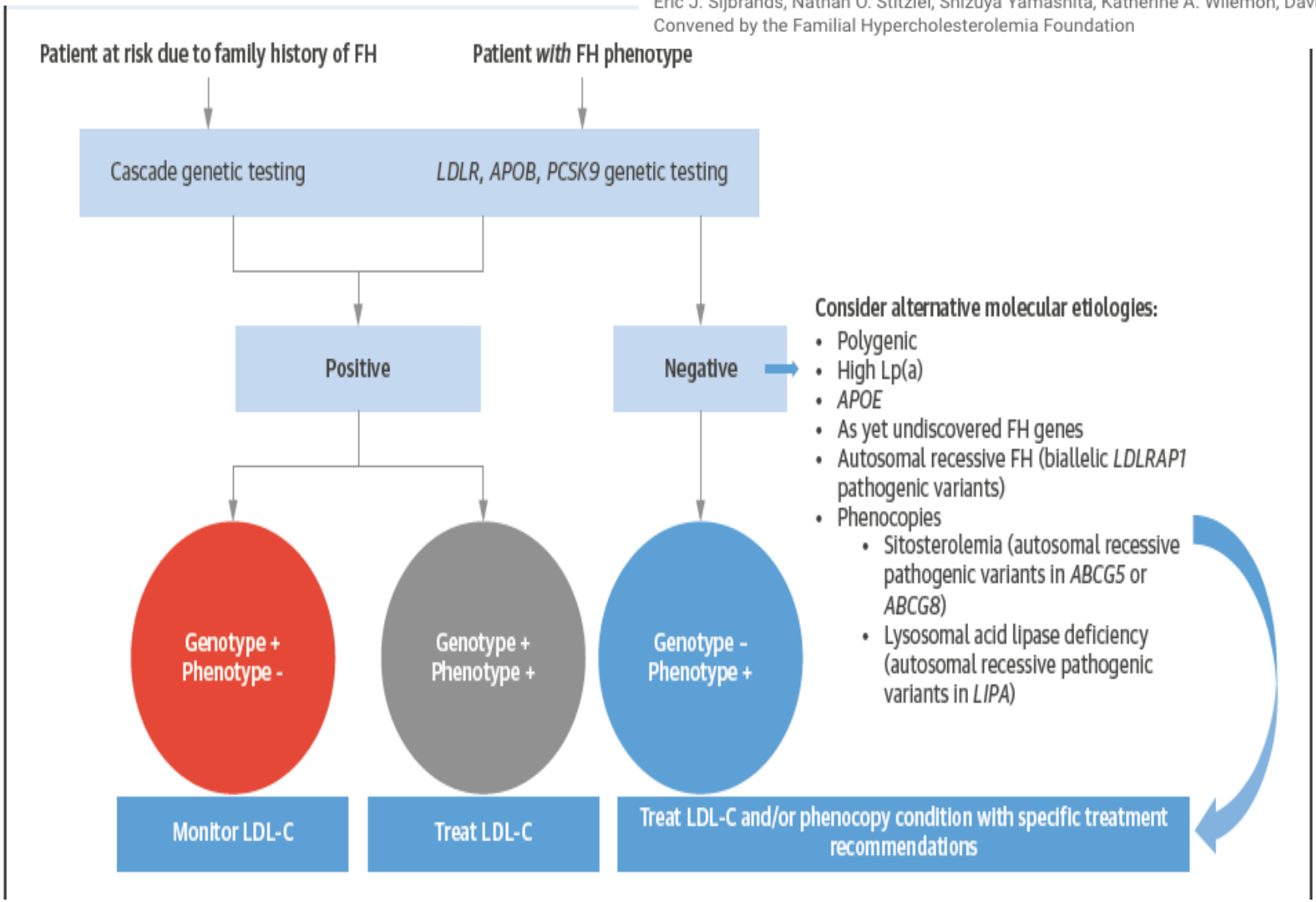
Graça R, et al. Manuscript under preparation

FH phenotype positive, genotype negative

- Worldwide about 50% of clinical FH cases do not have a putative pathogenic mutation in one of the three genes:
  - Familial combined hyperlipidemia (if apoB>120mg/dl)
  - Environmental dyslipidemia
  - Polygenic hypercholesterolemia (LDL score)
  - **Other monogenic lipid disorders (FH phenocopies, up to 5%)**
  - New FH genes (up to 5%)

FH recommendations consensus paper

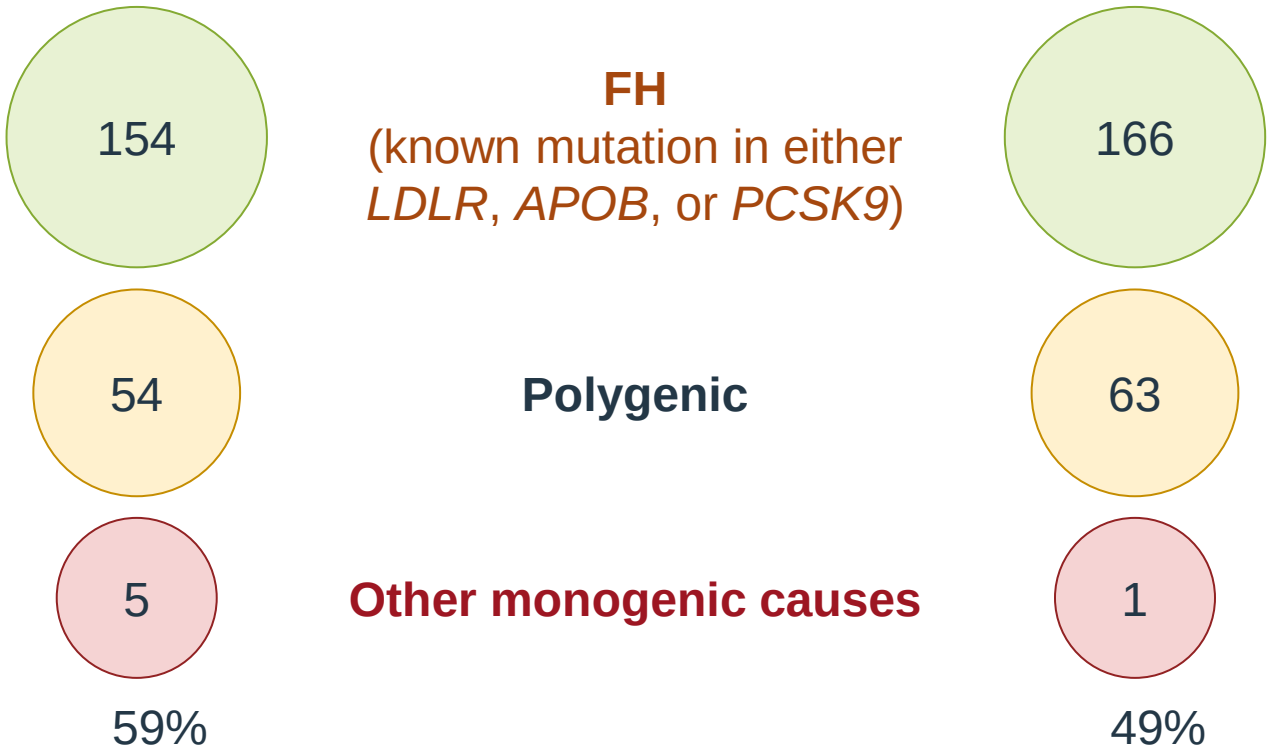
Clinical Genetic Testing for Familial Hypercholesterolemia
JACC Scientific Expert Panel
Amy C. Sturm, Joshua W. Knowles, Samuel S. Gidding, Zahid S. Ahmad, Catherine D. A
Seth J. Baum, Mafalda Bourbon, Alain Carrié, Marina Cuchel, Sarah D. de Ferranti, Joe
Ray E. Hershberger, G. Kees Hovingh, Lala Karayan, Johannes Jacob Pieter Kastelein,
E. Leigh, MacRae F. Linton, Pedro Mata, William A. Neal, Børge G. Nordestgaard, Raul
Eric J. Sijbrands, Nathan O. Stitziel, Shizuya Yamashita, Katherine A. Wilemon, David H
Convened by the Familial Hypercholesterolemia Foundation



Sturm et al, 2018 JACC

Portuguese FH study

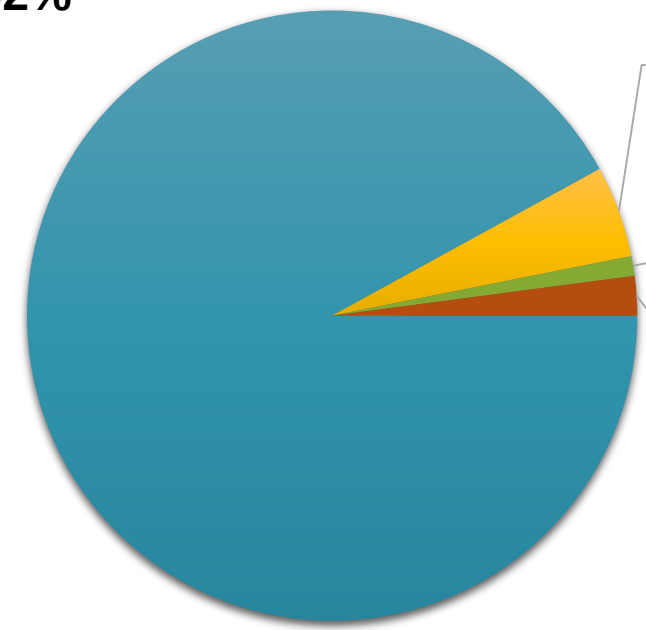
835 index cases from the Portuguese FH study



Mariano C, et al. Manuscript under preparation

Overall causes of monogenic dyslipidemia

- Overall, monogenic dyslipidemia is responsible for 39% (n=326/835) of all index cases with an FH phenotype



Other monogenic causes (*LIPA, ABCG8,, APOE*) are more common than ***PCSK9*** mutations

New NGS FH test – FH panel 8 genes:
LDLR, APOB, PCSK9, APOE, LIPA, LDLRAP1, ABCG5/8 + polygenic score

Mariano C, et al. Manuscript under preparation

From phenotype to genotype

FH phenotype	Disorder based on the genotype
Children (<16 years) Total cholesterol >260 mg/dL or LDL-C >155 mg/dL + family history of hypercholsterolemia	FH (LDLR, APOB, PCSK9)
	LAL-D (LIPA)
	Sitosterolemia (ABCG5/8)
Adults Total cholesterol >290 mg/dL or LDL >190 mg/dL + family history of hypercholsterolemia	Dysbetalipoproteinemia (APOE)
	Autosomal-recessive hypercholesterolemia (LDLRAP1)

From genotype to treatment

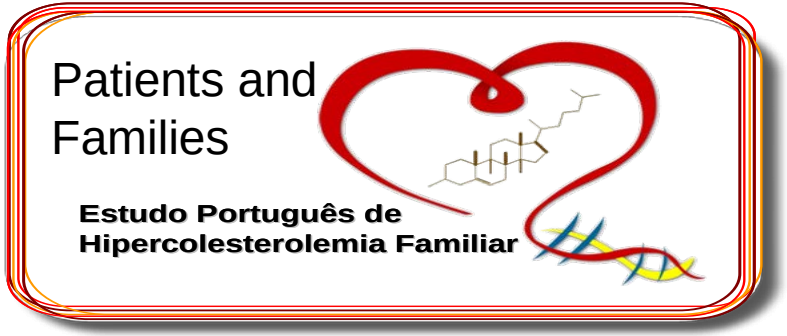
Familial hypercholesterolemia (htFH) **LDLR, APOB, PCSK9**	All FH patients 2nd generation statins and selective inhibitor of cholesterol absorption (combined therapeutic) Severe heterozygous patients add new PCSK9 inhibitors
Homozygous FH (true homozygotes) **LDLR, APOB, PCSK9** **Autosomal recessive hypercholesterolemia** **LDLRAP1**	Statins + iPCSK9 and/or LDL apheresis and/or MTTP inhibitor LDL apheresis
Dysbetalipoproteinemia **APOE**	Statins + fibrates
LAL-D **LIPA**	LAL replacement therapy
Sitosterolemia **ABCG5, ABCG8**	Diet poor on vegetal fat Inhibitor of cholesterol absorption

Familial hypercholesterolemia (FH)

The identification and characterization of the gene defect/pathway is important to establish a precise and personalized diagnosis and treatment

Acknowledgments

The Portuguese FH Study clinical investigators



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FCT Fundação para a Ciência e a Tecnologia

ALEXION

MRC Clinical Sciences Centre

Imperial College London

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My disclosures

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2006T102
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Erasmus MC
University Medical Center Rotterdam

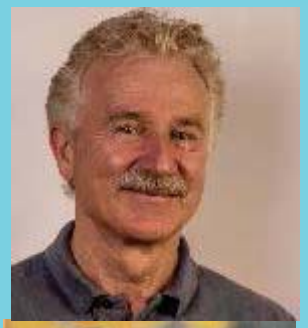
ICPerMed – FH program: Clinical Approach and Health System Implementation

Eric Sijbrands

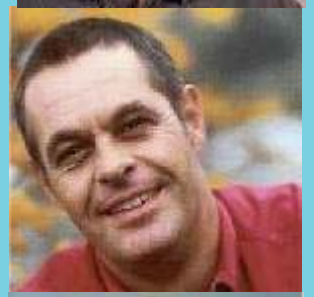
Section of pharmacology, vascular & metabolic diseases
Dept. of vascular genetics

Secret of successful national screening

John Kastelein



Joep Defesche



Peter Lansberg

Iris Kind

This presentation - outline

1. clinical presentation of FH
2. nation-wide FH screening program:
   - Why?
   - Who?
   - How?
3. any improvements?

When is the diagnosis FH considered?

premature coronary artery diseases

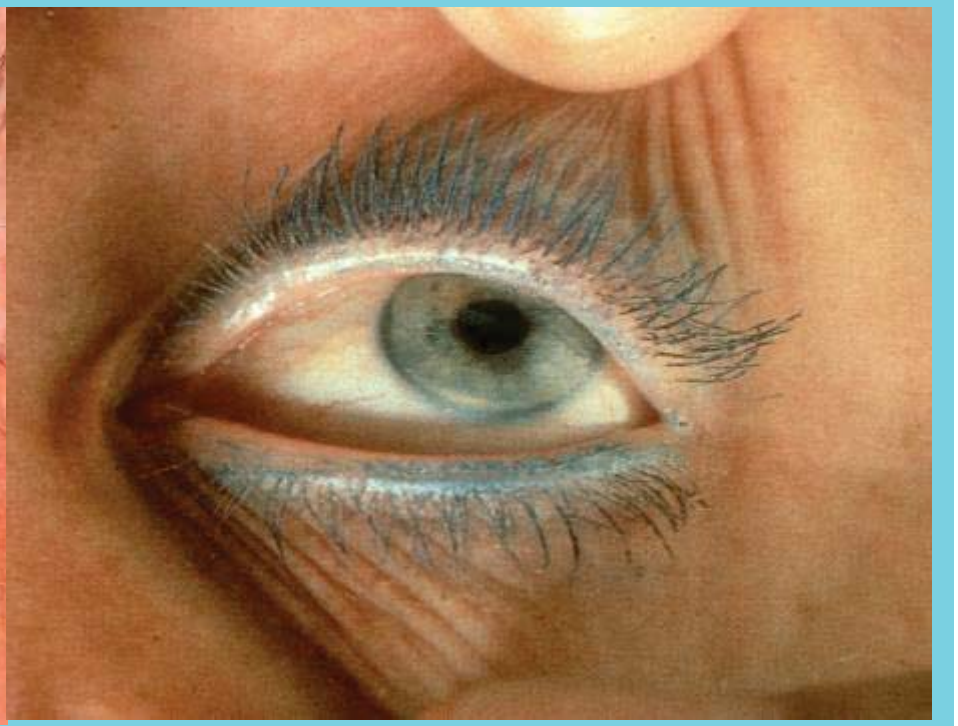
or

asymptomatic with severe hypercholesterolemia

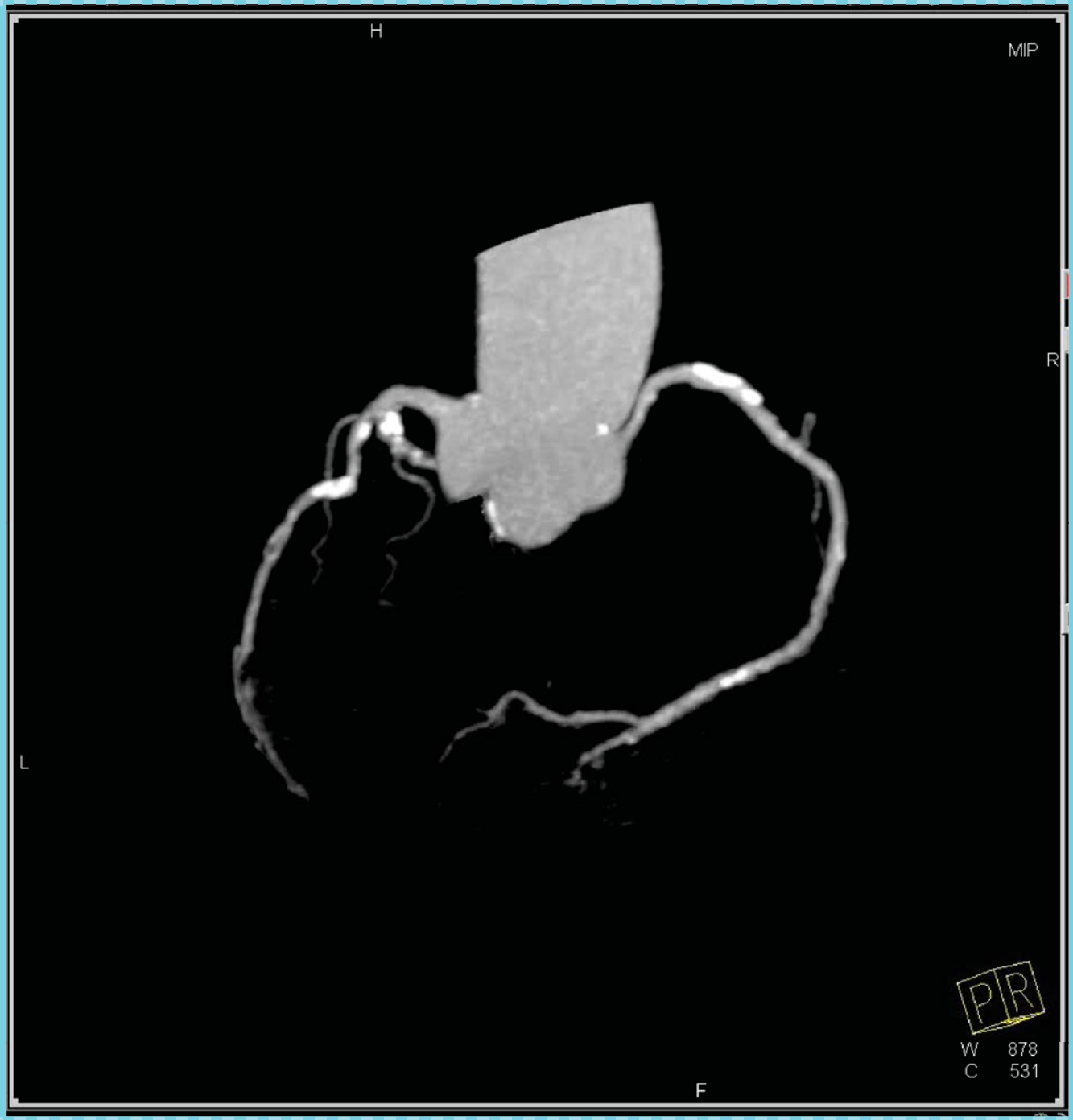
cholesterol	> 8.0 mmol/l (309 mg/dL)
LDL-cholesterol	> 4.9 mmol/l (90 mg/dL)

no secondary hypercholesterolemia

Clinical diagnosis



Clinical diagnosis



Erasmus MC

untreated
OR 8.5-13

large variation!

Adult index patient

Clinical diagnosis in proband

family history	
• First degree relative with premature CVD	1
• First degree relative with LDL > 95e percentile	
and / or	
• xanthomas or arcus	2
• kids < 18 jr. with LDL > 95e perc.	
personal history	
• premature CVD (men < 55, women < 60)	2
• premature CVA or peripheral vasc. disease < 60	1
physical examination	
• tendon xanthomas	6
• arcus (< 45 jr)	4
LDL cholesterol	
• > 8.5 mmol/l (> 330 mg/dl)	8
• 6.5-8.4 mmol/l (251-329 mg/dl)	5
• 5.0-6.4 mmol/l (196-250 mg/dl)	3
• 4.0-4.9 mmol/l (155-195 mg/dl)	1
DNA analysis	
• functional mutation in LDL receptor gene	>8

diagnosis proband:

certainly FH	**>8**
probably FH	**6-8**
possibly FH	**3-5**

↓

DNA diagnostics

↓

screening of family

Child index with hypercholesterolemia

LDL-C in age + sex specific 95th percentile

+

lean + normal TSH + dominant inheritance

↓

post-test probability = 0.95 (95% CI: 0.96-0.99)

Circulation 2011; 123:1167-73.

Genetic epidemiology

Mutations in the following genes:

1. *LDLR*
2. *APOB*
3. *PCSK9*
4. *APOE*
5. *BCG5/ABCG8* (sitosterolemia)
6. *LDLRAP1* (autosomal recessive)
7. Polygenic SNP-score

Statin treatment

Erasmus MC

early diagnosis

↓

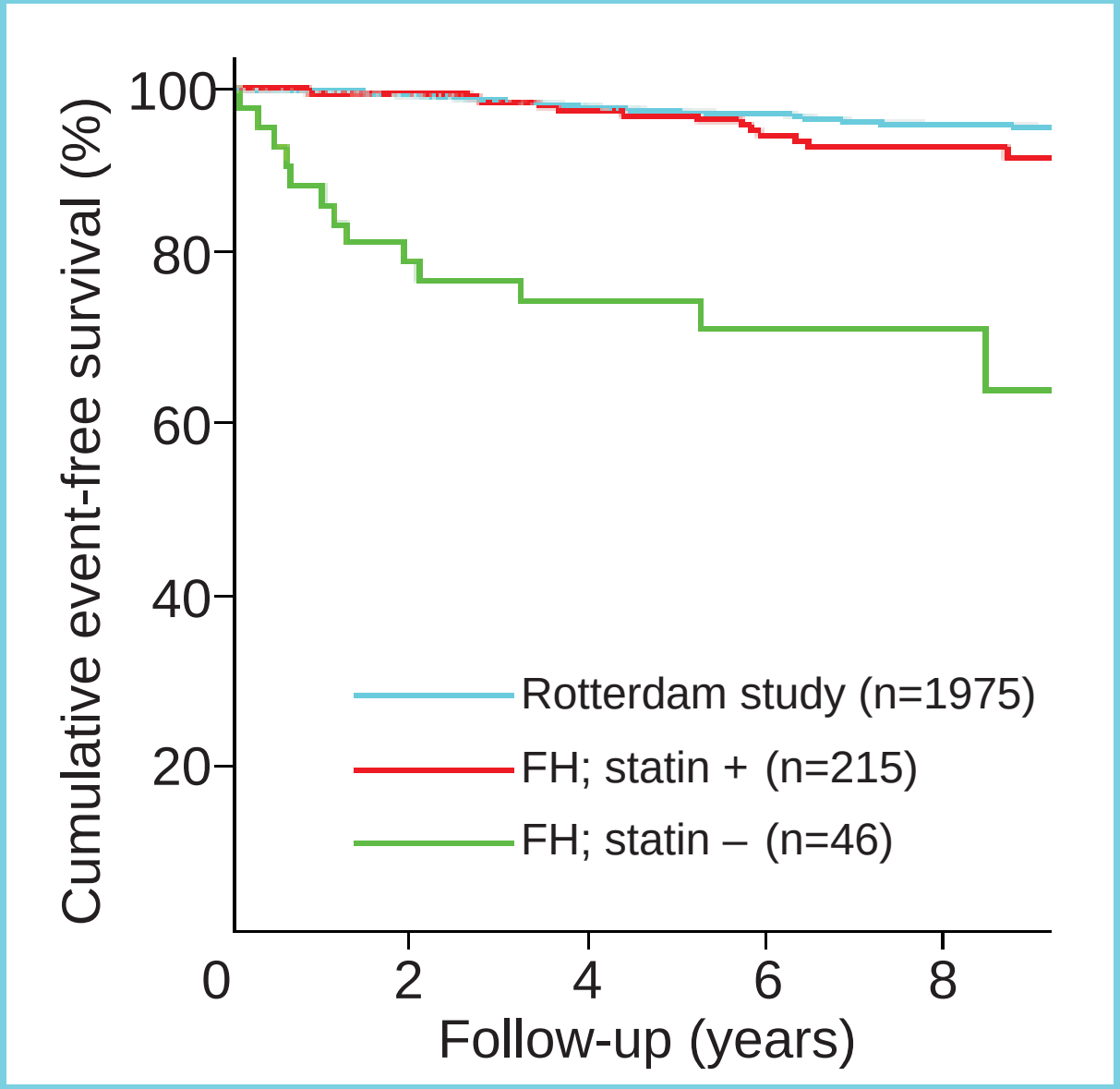
CHD reduction in statin-treated FH

		Model I		*Model II*
	No	**HR (95% CI)**		**HR (95% CI)**
All	1950	0.24 (0.18-0.30)		0.18 (0.13-0.25)
Male	924	0.20 (0.15-0.28)		0.17 (0.11-0.26)
Female	1026	0.30 (0.20-0.43)		0.21 (0.13-0.34)

Model I *adjusted for sex and year of birth*
Model II *+ smoking, hypertension, diabetes, HDL-C and LDL-C*

BMJ 2008;337:a2423.

Rotterdam study vs untreated and treated FH



HR 1.44; n.s.

HR 8.69; p<0.001

Cost-effectiveness of cascade screening

Country	Sequencing Index	relative	Costs per patient	Costs/life year saved
NL2002	700	107	1200	8700
Spain	600	100	n.a.	26000
UK-EHR of GP	450	135	n.a.	7750
UK-cascade	450	135	n.a.	7690

Sem Vasc Med 2004;4:97.
J Clin Lipidol 2017;11:260-271.
Atherosclerosis 2018;275:80e87.

Screening

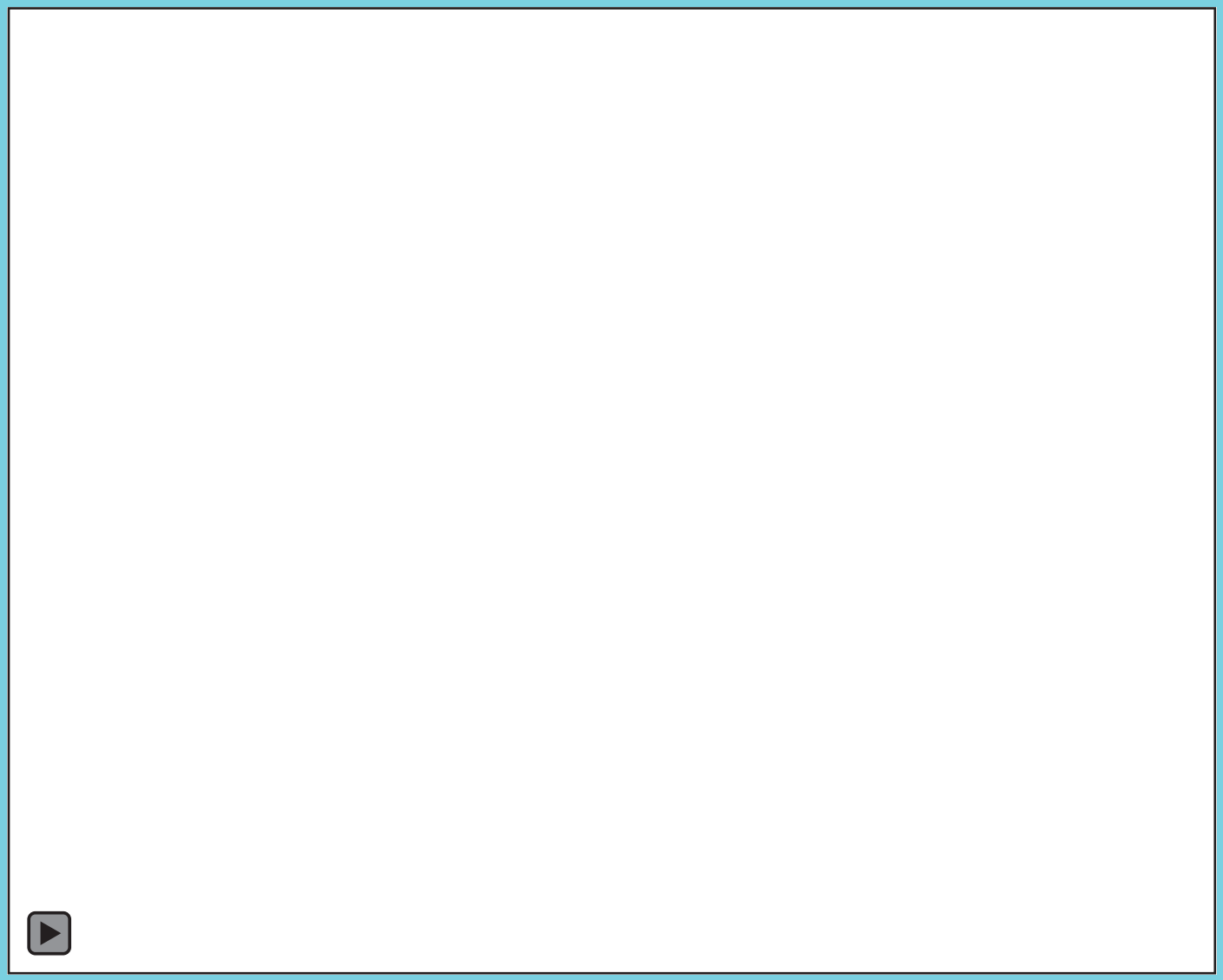
Erasmus MC

enough info for a molecular diagnostic screening program?

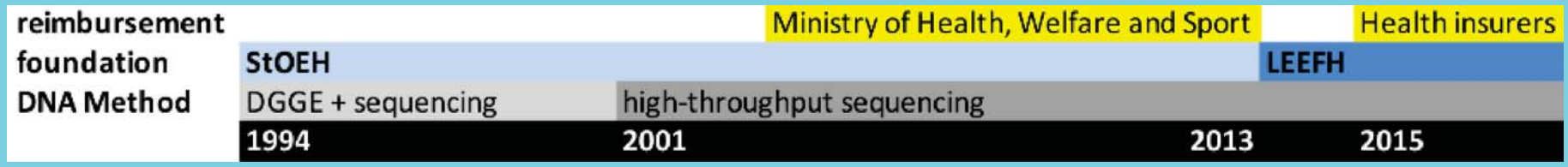
Why shouldn’t you screen for FH?

1. severe premature complications
2. no prodromes
3. treatment available
4. good cost-effectiveness
5. whose responsibility…?
6. insurance companies guarantee insurability
7. patient support group

Cascade screening



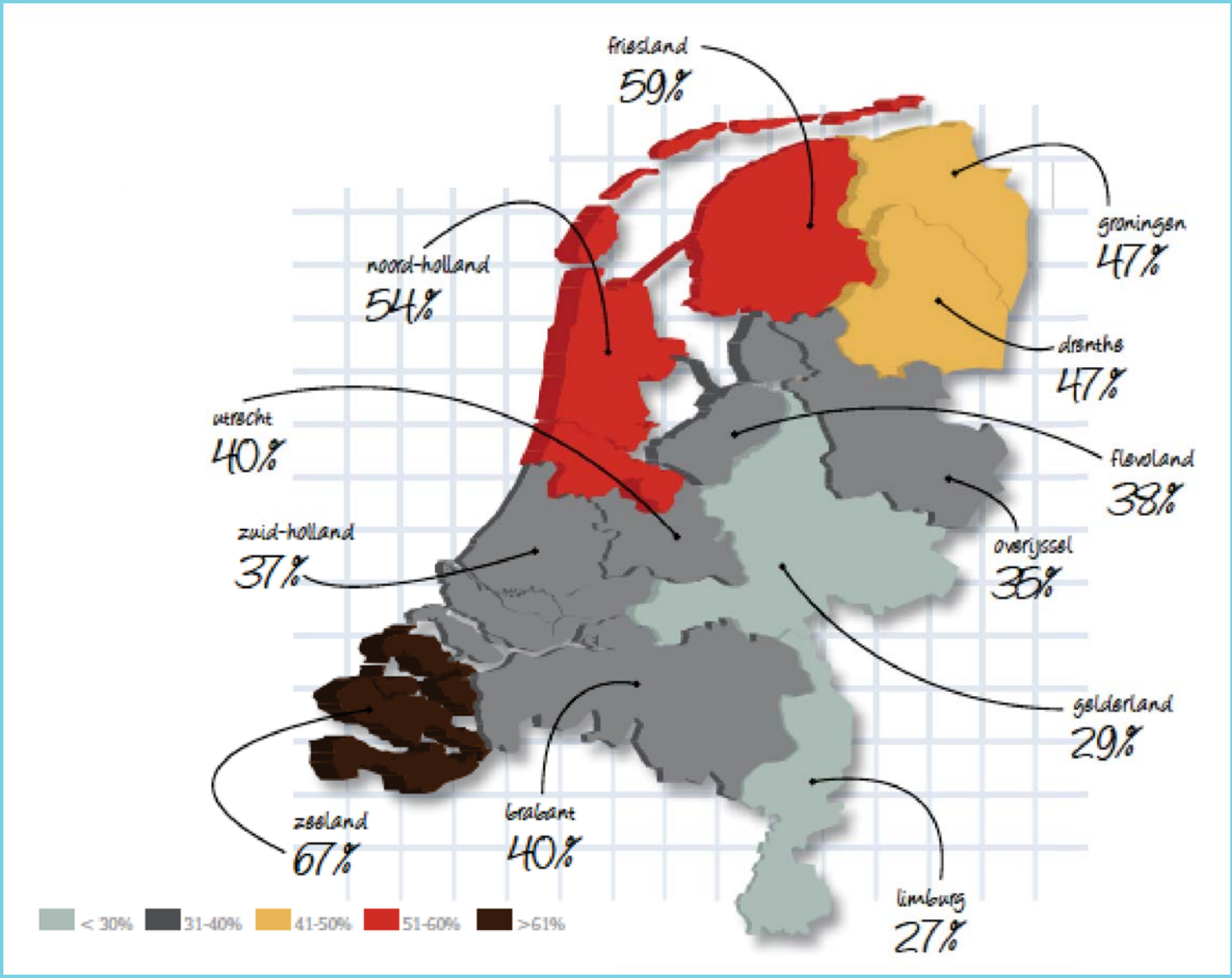
History of Dutch FH screening



550 patients/year >2000 patients/year

>30.000 patients with mutation identified

% identified (prevalence 1:240)

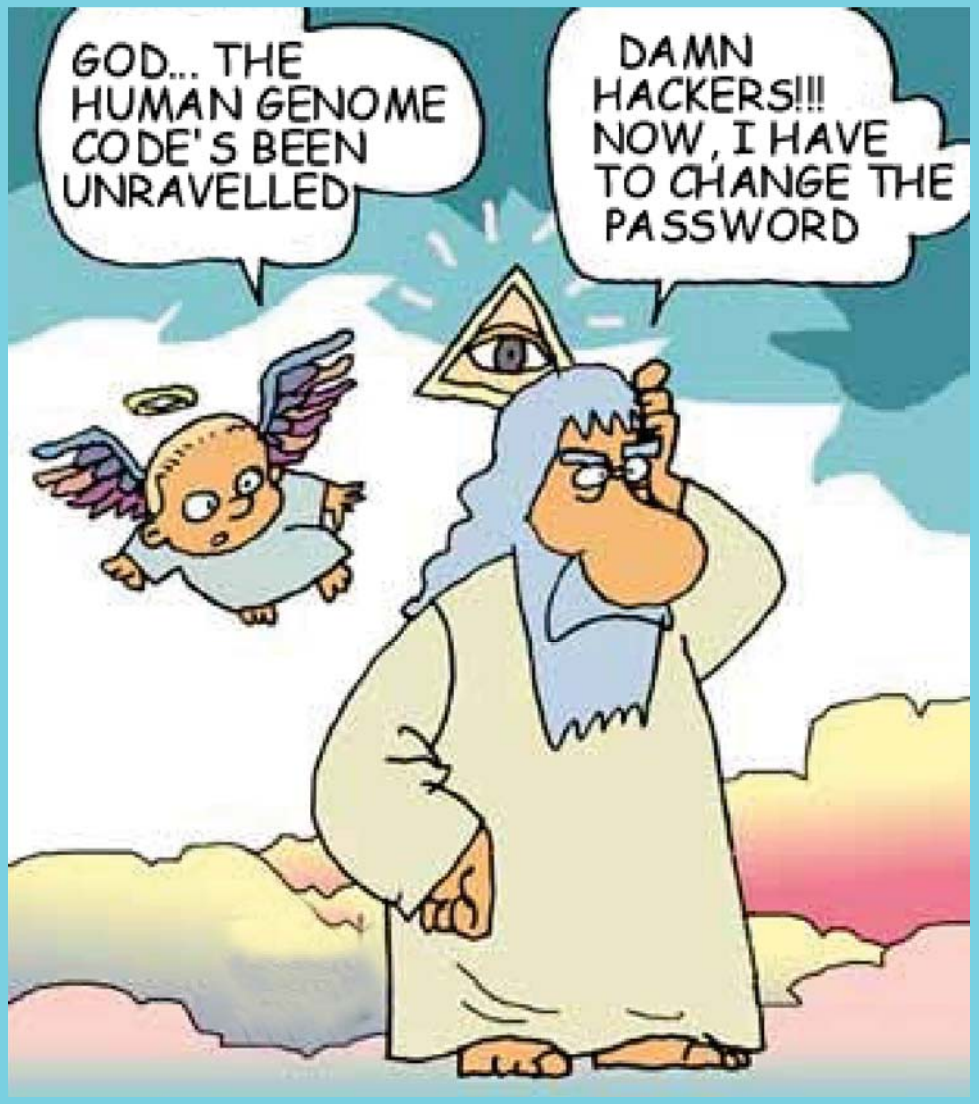


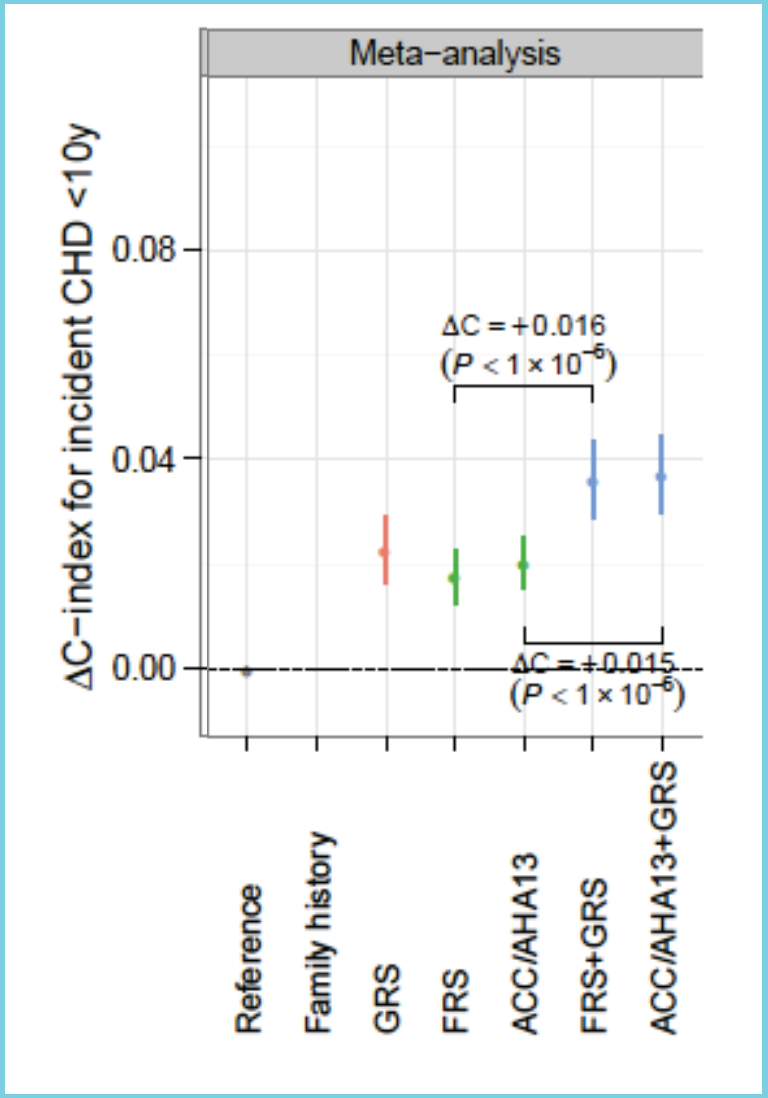
How to improve?

Large variation of risk in untreated FH
Residual risk in treated FH

Better risk prediction
New drugs
Personalized approaches

Genomic Risk Score (GRS)





Abraham, et al. Eur Heart J 2016;37:3267-78.

Genomic Risk Score (GRS)

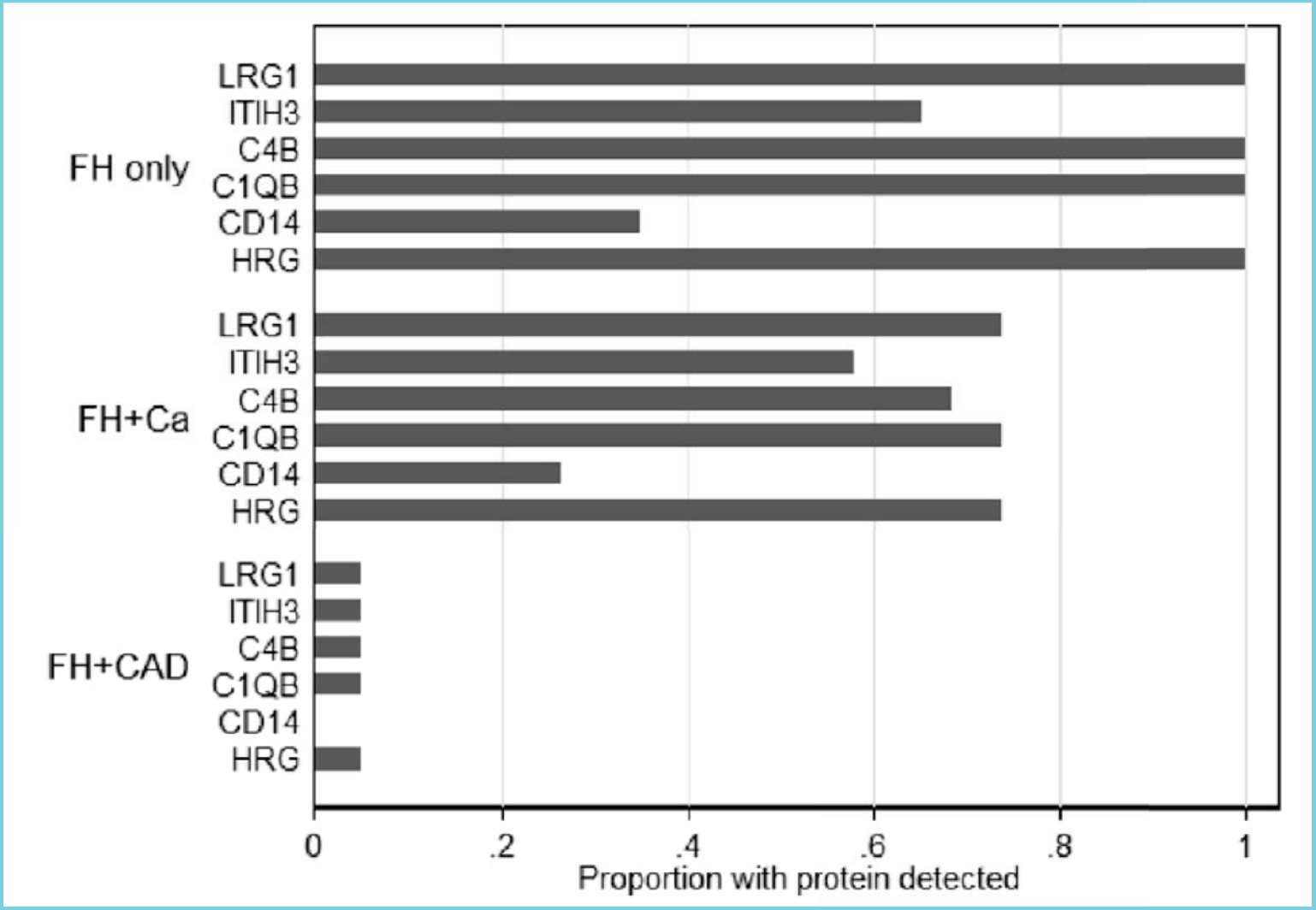
1. low RR
2. non-smoking
3. low cholesterol

↓

compensate for high GRS

Abraham, et al. Eur Heart J 2016;37:3267-78.

Proteomics



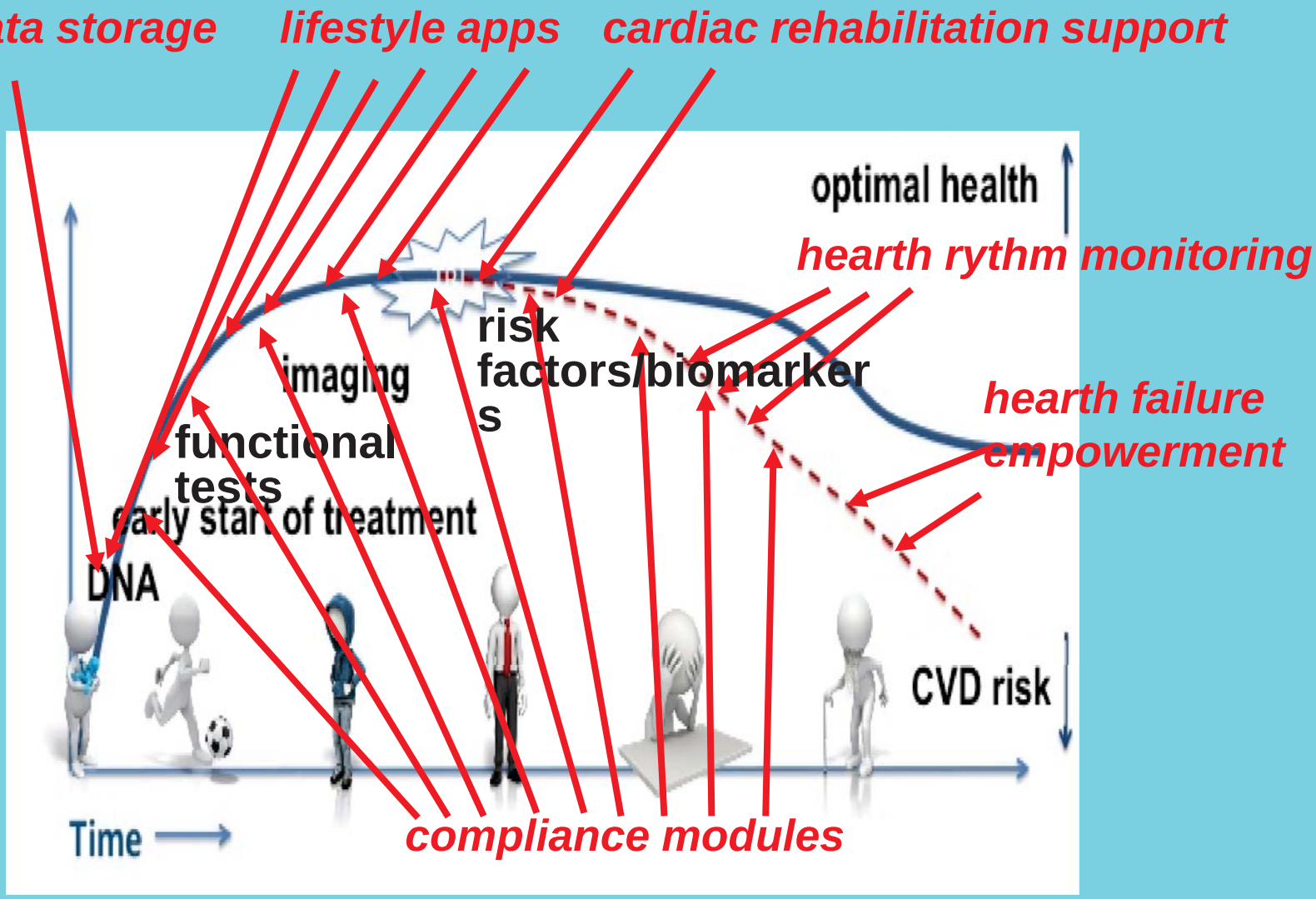
Bos, et al. J Clin Lipidol 2017;11:682-93.

Conclusions

improve screening by adding GRS

monitor effect of treatment with functional tests like the signals from healthy vessels

Future: tailored life course health and care



EIT Health: SkyCare; PPP's

FH - The key issues

Steve Humphries. : Emeritus Professor Cardiovascular Genetics UCL. Medical Director StoreGene

British Heart Foundation

- **It is Common - Frequency FH ~1/270**

  Predict > 200,000 in UK, ~2,000,000 in EU

- **It is underdiagnosed - < 10% of predicted UK known in most of EU**

  particularly in the < 35 years group

- **It runs in Families - autosomal dominant trait so 50% of children of an FH parent will have FH**

  Cascade testing →find more FH patients

- **50% of men will have MI by age 50 years, and 60% of women by age 60 years**

  Early treatment with Statins reduces CHD risk

- **Statin treatment very safe and cost effective**

  Many identified patients are under treated

FH is a disorder of LDL-Clearance from the blood

FH Diagnostic criteria

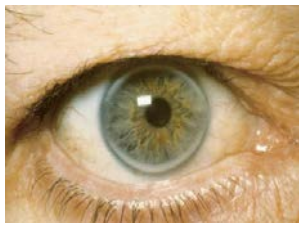
Simon Broome FH Register criteria:

- Cholesterol > 7.5mmol/l or LDL > 4.9mmol/l in adult
- Cholesterol > 6.7mmol/l or LDL > 4.0mmol/l if < 16 yrs
- PLUS family history of high cholesterol or MI (<55yrsM)
- OR PLUS Tendon Xanthoma
- OR FH-causing mutation

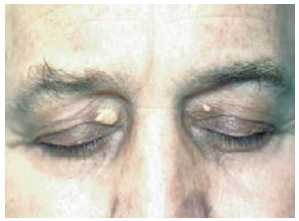
Possible FH

Definite FH

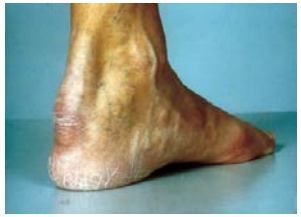
Corneal Arcus

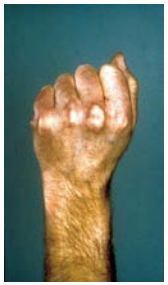


Xanthelasma



Tendon Xanthoma





Also Dutch Lipid Clinic Criteria scoring system & US system MEDPED

Dutch Lipid Clinic Network Criteria		Points
Family history	1st-degree relative with known CVD (M <55yrs/F<60yrs)….	1
	1st-degree relative with TX and/or arcus cornealis,…..	2
Clinical history	Patient with premature CHD	2
	Patient with premature stroke or PVD	1
Physical examination	Tendon xanthomata	6
	Arcus cornealis prior to age 45 years	4
LDL-C levels	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
DNA analysis	Functional mutation in the LDLR gene	8

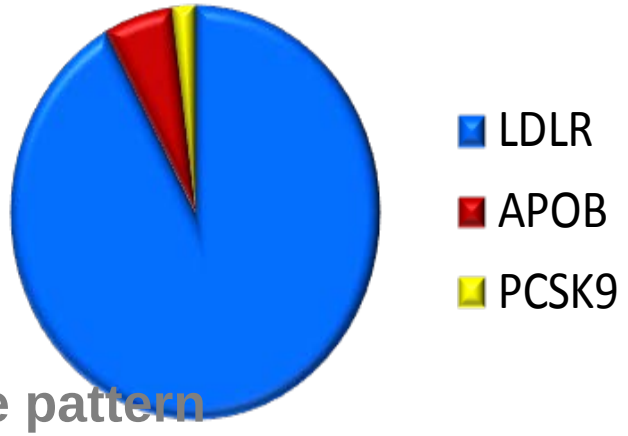
>8 points = Definite FH
6 - 8 = Probable FH
3 - 5 = Possible FH

Welsh include –ve points for high TG – Haralambos et al 2014

Genetic Causes of FH

Iacocca et al Hum Mut 2018

- *LDLR* – Commonest cause > 1700 world wide and >300 in UK
- *APOB* – One common mutation p.R3527Q
- *PCSK9* – Gain-of-Function - Least frequent but most severe cause
- *APOE* - Leu167del frequency unknown
- *LIPA* - homozygosity → recessive pattern
- *LDLRAP1* – homozygosity (stop) – recessive pattern



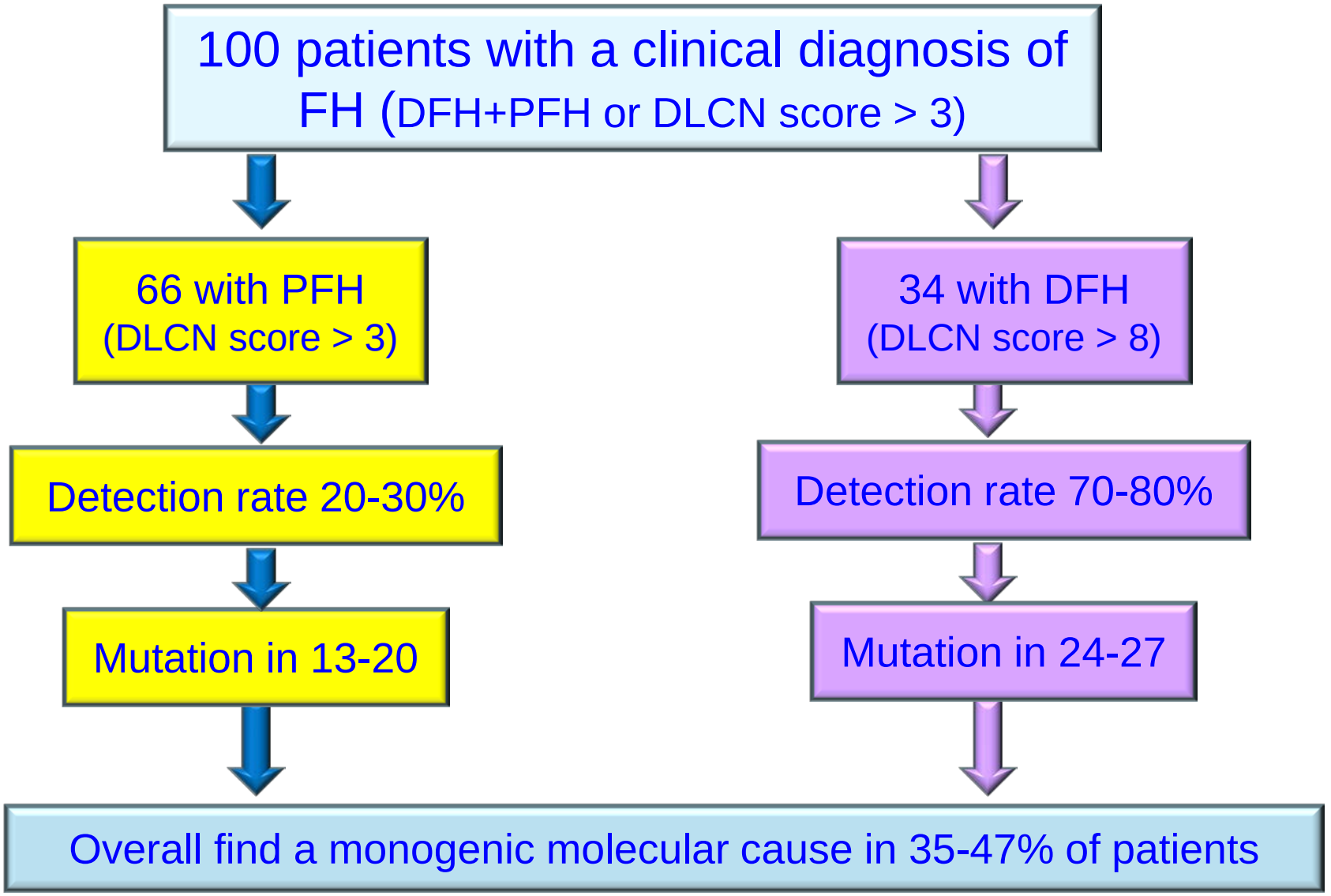
DNA tests for FH - Offered by all 7 UK NHS Diagnostic Genomic Hub Labs

- Use NGS to capture and sequence exons of all genes in one run
- 96 samples can be handled in one run
- Costs now ~£250 for an index case, single mutation in relative ~ £70.
- Time taken to report now 4-6 weeks
- Costs of tests covered by NHS England from April 2019

What is mutation detection rate?

What is overall mutation detection rate?

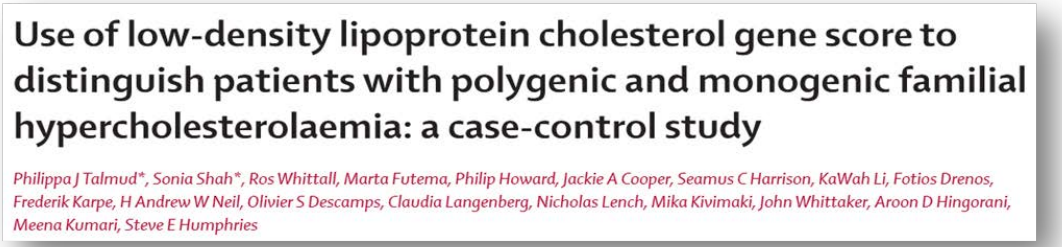
Taylor et al Clin Genet 2010



Polygenic Cause of no mutation FH

Hypothesis: Having large number of common genetic variants that each raise LDL-C by small amount could mimic Monogenic FH

Talmud et al Lancet 2013


Use of low-density lipoprotein cholesterol gene score to distinguish patients with polygenic and monogenic familial hypercholesterolaemia: a case-control study

Philippa J Talmud*, Sonia Shah*, Ros Whittall, Marta Futema, Philip Howard, Jackie A Cooper, Seamus C Harrison, KaWah Li, Fotios Drenos, Frederik Karpe, H Andrew W Neil, Olivier S Descamps, Claudia Langenberg, Nicholas Lench, Mika Kivimaki, John Whittaker, Aroon D Hingorani, Meena Kumari, Steve E Humphries

- Used 12 common LDL-Raising DNA variants (SNPs) to make an "LDL-Gene Score"
- Compared score in mutation -ve FH patients,vs 3000 healthy subjects
- **Results :** Significantly higher mean score in M-ve FH vs Controls
- **Conclusion :** In at least 80% of M-ve patients a "polygenic" cause of their elevated LDL-C is most likely explanation
- Results confirmed in samples from 9 other countries

Only those with a detectable mutation should → a diagnosis of "FH" – others "Polygenic Hypercholesterolaemia"

Why is the polygenic explanation important?

- **Research:** Searching for a new gene causing FH in high score patients will not be successful!!!

500 no mutation/low score FH patients in 100,000 Genome project

https://www.genomicsengland.co.uk/the-100000-genomes-project/

- **Money :** Cascade testing in monogenic FH → 50% first degree relatives will be FH. BUT in polygenic hypercholesterolemia → fewer than 30% "affected" relatives - ie much less cost effective

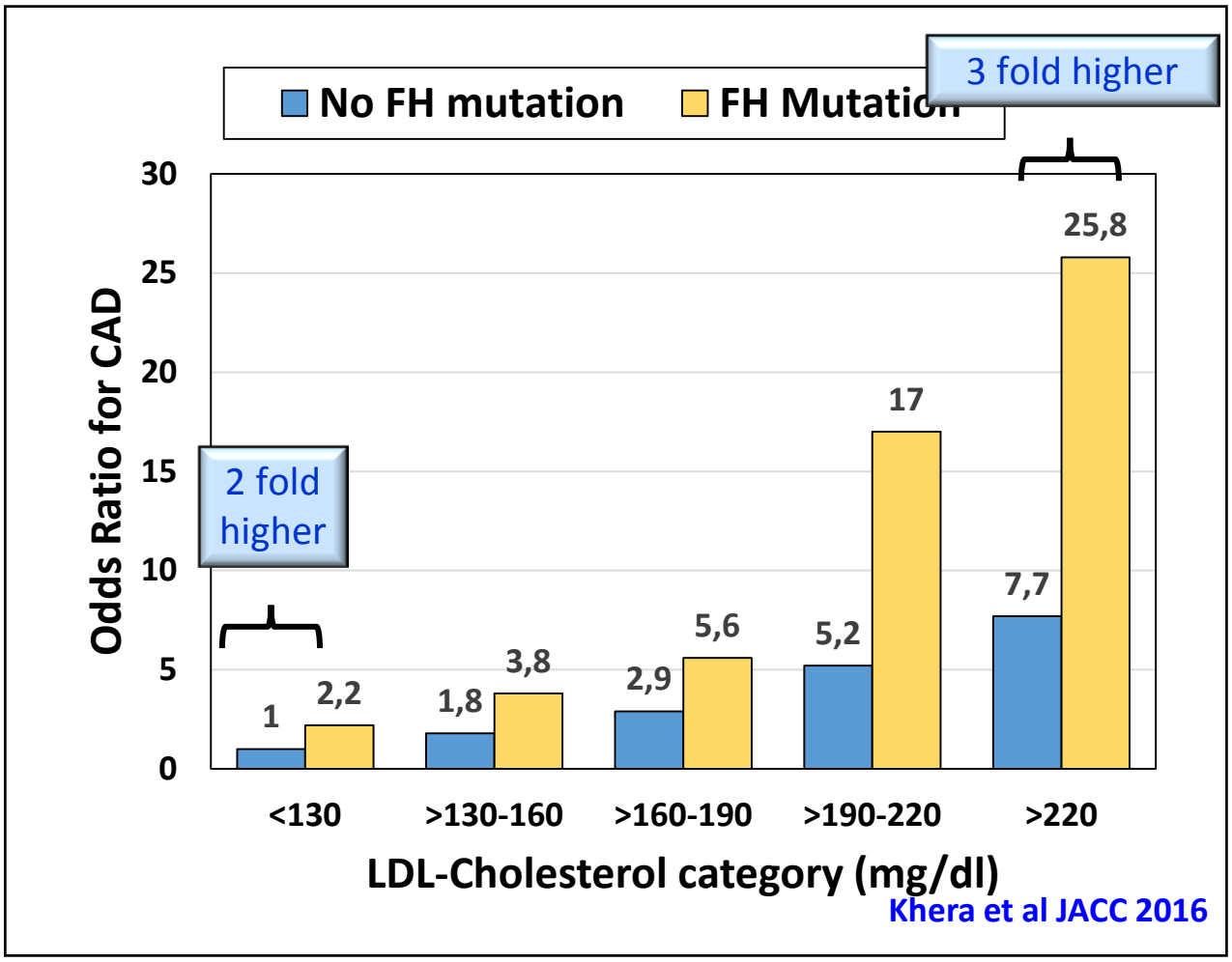
- **Treatment :** Monogenic FH have high CHD risk and need to be managed by lipid clinics, BUT polygenic FH patients have less severe CHD and can be managed by statin treatment by GPs (not expensive tertiary referral centres)

What is evidence for higher CHD in monogenic FH?

> CAD risk in Monogenic ve Polygenic high LDL-C

Khera et al JACC 2016

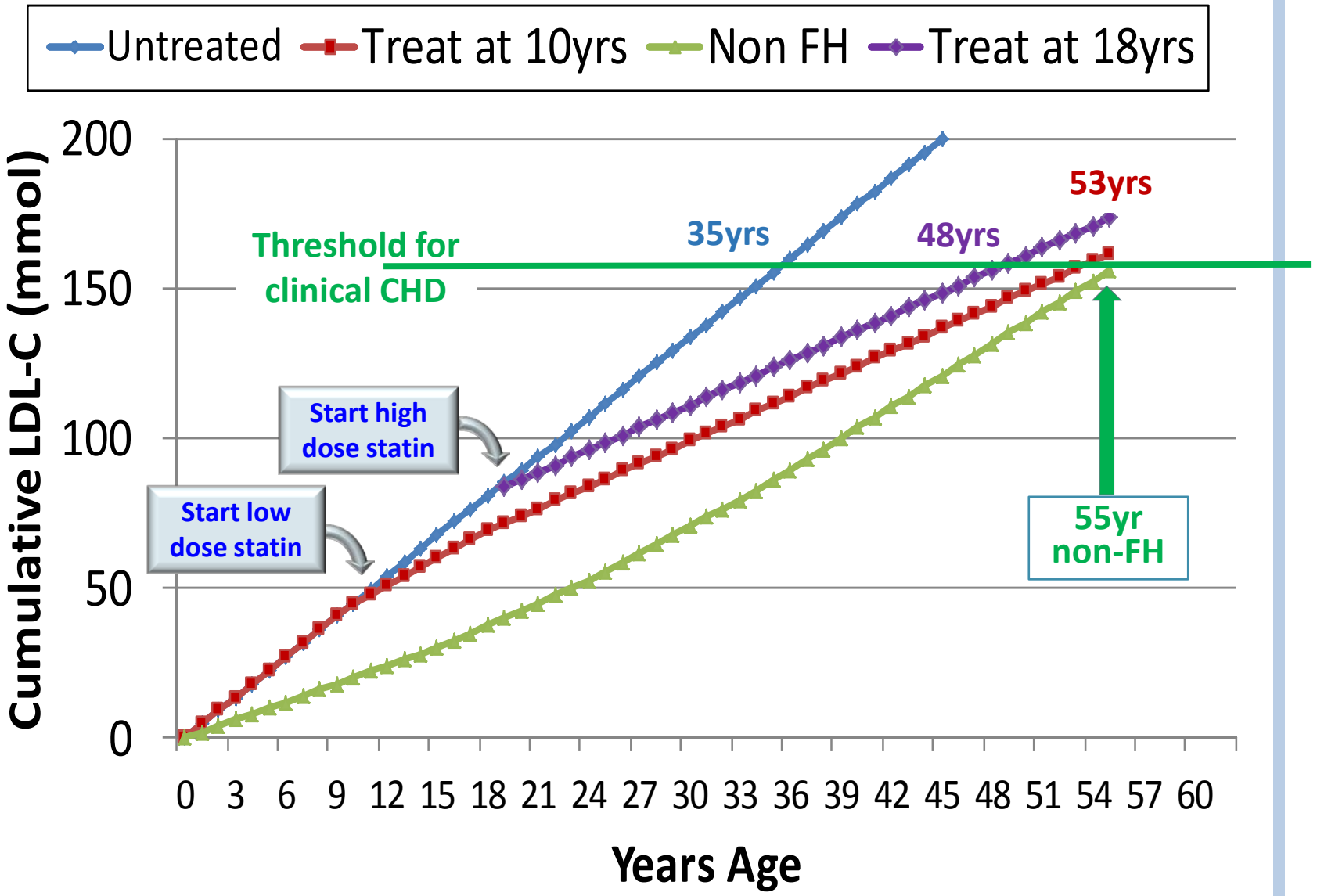
- Among 20,485 CAD-free control and prospective cohort participants,
- 1,386 (6.7%) had LDL-cholesterol ≥ 5.0mmol/l
- of these, 24 (1.7%) carried an FH mutation.



Within any stratum of LDL-C, risk of CAD was 2-4 fold higher among FH mutation carriers than non-carriers.

Mechanism :
FH mutation = life-long exposure to elevated LDL-C.
→ higher CAD risk than in those with a polygenic "late rising" of LDL-C

LDL "Burden" = ∑measured LDL-C x age

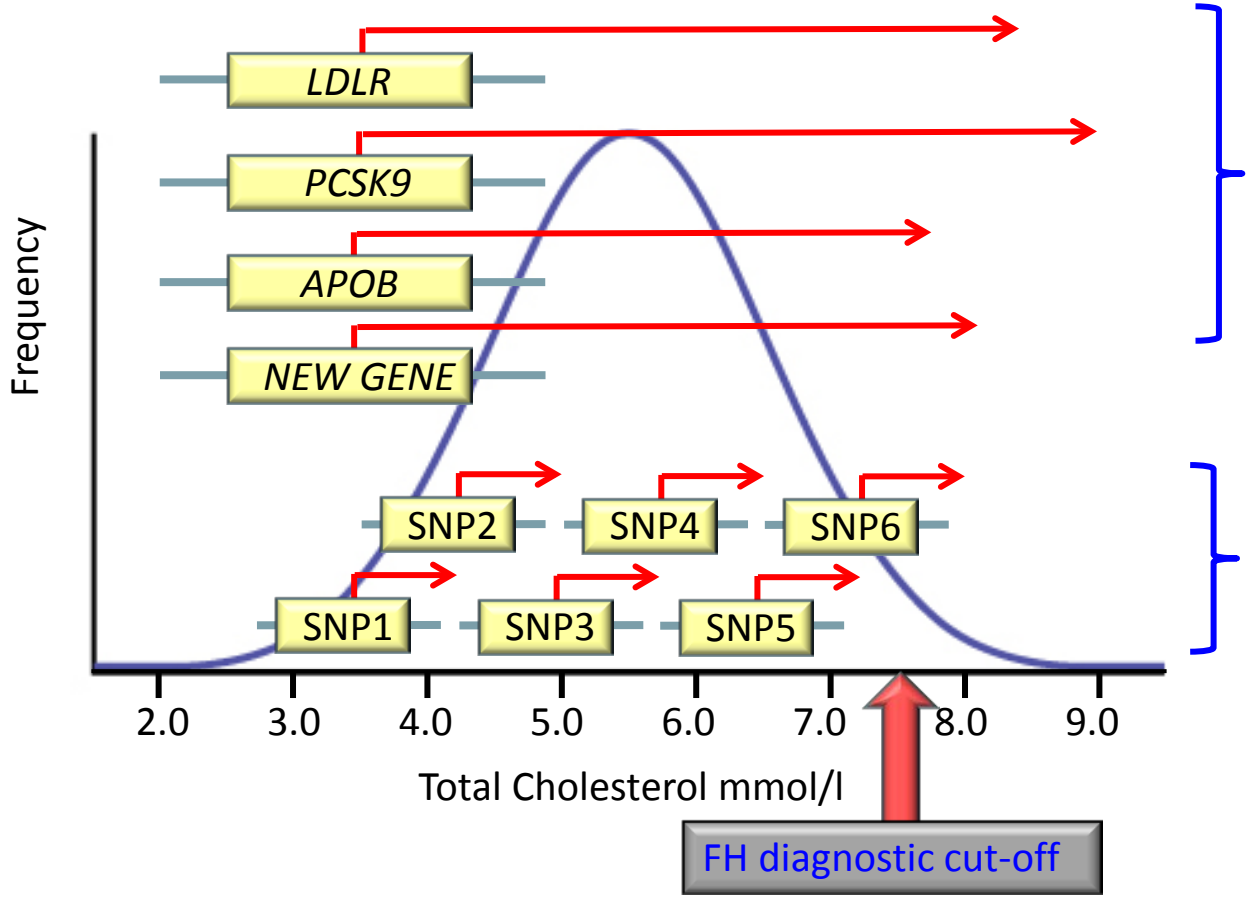


Guidelines → "Consider statin by age 8/10yrs.." to reduce premature CHD burden

Monogenic & Polygenic causes of high Cholesterol

You can be above diagnostic threshold because of :

1. having a pathogenic mutation in a single gene or by
2. the combination of > average number of common variants



High CHD risk. Treat with high intensity statins in lipid clinic

Lower CHD risk. GPs to use QRISK to estimate CHD risk and treat

Paradigm example of Genomic information → Precision Medicine

Commercial availability for FH DNA tests

Test must include:

- NGS for whole of *LDLR/APOB/PCSK9/APOE/LDLRAP1*
- Plus 12 LDL-C Score SNPs
- Plus ACMG criteria for Variant calling
- Report in 4 weeks from sample receipt

Bristol NHS lab charges £400 |

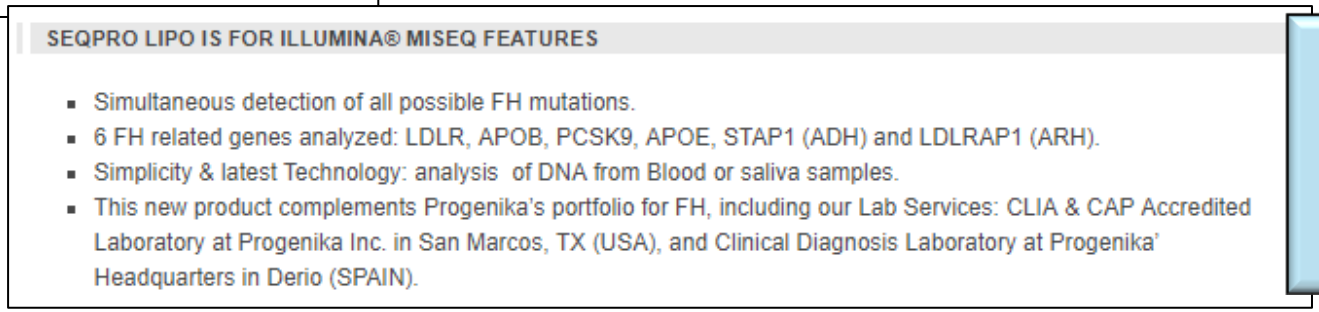
color

http://www.color.com

Saliva Sample. Sent by HCP or DTC. NGS of exons of *LDLR/APOB/PCSK9*. Only ACMG 4/5 variants reported Genetic councillor by phone

Progenika Biopharma
GRIFOLS

http://www.progenika.com/



DNA/Blood or Saliva. Only accept from HCP NOT DTC. NGS of exons of all genes. Price ??

Commercial availability for FH DNA tests

Quest Diagnostics

https://www.questdiagnostics.com/

Genetic testing for FH, from Quest, examines 3 actionable[2-6] FH genes: LDLR, APOB, and PCSK9, to enable an early, definitive diagnosis of FH. Early testing, both in adults and in family members, through cascade screening, can lead to early

HCP and DTC
Costs,turnaround and coverage unclear

INVITAE

https://www.invitae.com/

Primary panel (4 genes)

APOB | LDLR | LDLRAP1 | PCSK9

Panel details and technical assay limitations

$250
3mls Blood or Saliva
2-3 weeks

CENTOGENE
THE RARE DISEASE COMPANY

https://www.centogene.com/

NGS Panel + CNV

LDLR/APOB/GHR/PCSK9

Turnaround Time:	25 business days
Coverage:	~98-99% covered >20x
Required Material:	≥1ml EDTA Blood or

Cost unknown
Blood spots on card and post or blood
2-3 weeks

Summary : Plenty of testing companies around the world. Many websites unclear about Methods, Cost, Turnaround, and after test counselling.
No company currently offers 12 SNP score

ICPerMed Conference 2018

Third best practice example:
Translational medicine in familial hypercholesterolemia – from phenotype to genotype to treatment

What is the PATIENT BENEFIT?

Gabriele Hanauer-Mader
President Patient Organization FHchol Austria
Vienna

Familial Hypercholesterolemia

Genetic Disease with more than 2,000 identified pathogenic mutations

It is:

UNDERESTIMATED

UNDERDIAGNOSED

UNDERTREATED

despite potent & effective therapies and a Nobel Prize in 1985 describing the genetic mechanisms of the condition that leads to heart attacks & strokes if not treated

From personal suffering to the collective mission

2004: First FH patient advocacy group in the German-speaking countries

2011: Kick-off for two individual patient organizations in Austria and Germany that cooperate very closely

Personalized medicine – what is it?

- **It is not:** a more personalized relationship between physician & patient – as much as needed at times. Patients sometimes misunderstand this.
- Focus of personalized medicine lies on the **consideration of patients‘ individual properties** – in diagnosis, therapy, and prevention
- In particular: **patients‘ molecular biological properties** that can be determined by biomarkers

Patient benefit through personal medicine

Biomarkers are invaluable

- when it comes to deciding which therapy the patient needs or responds to
- when it comes to reduce or avoid therapies‘ side effects – in FH patients e.g. statin intolerance
- Up-to-date molecular data analysis may even lead to the development of new therapies for currently not treatable rare diseases

Personalized Medicine & Prevention

- There is great hope that personalized medicine will in the long run usher in a new era in the **PREVENTION** of diseases and secondary diseases – in the case of familial hypercholesterolemia cardiovascular diseases like heart attacks and strokes

Personalized medicine & patient organizations

- Interdisciplinary cooperation between scientists, clinicians and patients is pivotal and fruitful = POWERFUL TEAM
- Especially on ethical issues – e.g. protection of sensitive (genetic) data in line with strict data protection laws – patient organization can add valuable advice
- It‘s the patients that can best claim patients‘ rights vis-a-vis stakeholders and public health authorities

Personalized medicine & patient organizations

- Empowered patients raise awareness of their conditions
- Patients do have an important voice – they are the faces of their conditions
- Through national and international registries patient data can be evaluated in favor of patients‘ optimal treatment according to their genetic profile – „the right drug to the right person“

FHcholAustria

Austrian FH Registry currently stores data of approx. 400 patients

FHcholAustria

Patient Organizations and the Medical & Science Community:

Perfect Team in Personalized Medicine

What can patients do?

Liaise closely with media via press conferences, awareness events, etc.

Patient Testimonials are pivotal

Lena-Rosa (18) mit Stoffwechselspezialist Prof. Stulnig, AKH Wien, bei einer Besprechung. Die Schülerin hat ihre Krankheit gut im Griff.

„Wir leben sehr bewusst!"

Wie zwei junge Patientinnen ihre angeborene Fettstoffwechselstörung FH meistern und warum ein Bluttest ganze Familien retten kann

Bei einer Routineuntersuchung zeigte das Blutbild der damals zweijährigen Marie-Violeta abnorm hohe Gesamt-Cholesterinwerte an – fast 300 mg/dl. Am Befund stand die lapidare Bemerkung: „Weniger Fett essen." Die besorgte Mutter Christiane P. („Mein Kind wurde immer sehr gesund ernährt, ich habe nur dampfgegart.") konsultierte sofort den Hausarzt, der meinte, das müsse man zwar kontrollieren, aber keinesfalls Medikamente geben. Das Gleiche passierte beim Internisten. So begann die Deutschlehrerin zu recherchieren und stieß auf die Patientenplattform www.fhchol.at.

Das änderte alles: „Obfrau Gabriele Hanauer-Mader hat uns zum Spezialisten dirigiert und mir alle wichtigen Details über die angeborene Stoffwechselerkrankung meines Kindes erklärt." Diagnose: Familiäre Hypercholesterinämie, FH.

Es handelt sich um eine der am meisten verbreiteten Erbkrankheiten, bei der ein Defekt der Rezeptoren des LDL-Cholesterins vorliegt – der Wert steigt und damit die Gefahr für Gefäßschäden bis zu frühem Herzinfarkt und Schlaganfall.

Marie-Violeta ist jetzt 8 Jahre alt, ein aufgeweckter Wirbelwind, der gerne läuft, im Abenteuerturnsaal herumtobt, Handball spielt, Mathe und Sachunterricht liebt. Sie hält fettreduzierte Diät, steht unter ärztlicher Kontrolle. Bei Wachstumsschüben und in Zeiten von Hormonveränderungen muss die Therapie angepasst werden.

Ernährungs- und Bewegungsprogramme

Marie: „Es nervt schon manchmal, wenn die anderen Kinder glauben, ich mag die Speisen im Hort nicht – dabei darf ich halt nicht alles essen. Aber an besonderen Tagen gibt es Ausnahmen! Mir schmeckt sowieso nur Karottentorte."

Das hat auch Lena-Rosa Hanauer so erlebt. Die bildhübsche 18-Jährige wird im kommenden Jahr maturieren und möchte Biomedizin studieren. Sie bekam die Diagnose FH ebenfalls als kleines Mädchen, wurde medikamentös eingestellt, erhielt Ernährungs- und Bewegungsprogramme. Im väterlichen Familien-Zweig traten gehäuft Herzinfarkte in jungen Jahren auf, auch bei ihrem Vater.

„Als ich erfuhr, dass meine Tochter eine gefährliche Fettstoffwechselkrankheit hatte, wusste ich nicht, wohin ich mich wenden und wer uns helfen sollte", erinnert sich Mama Gabriele Hanauer-Mader. Mühevoll trug sie Informationen aus anderen Ländern zusammen – daraus entstand 2004 die Gründung der Patientenorganisation FHchol Austria, der die engagierte gelernte Übersetzerin aus Wien vorsteht.

„Ich fühlte mich immer wieder einmal eingeschränkt, aber man muss eben damit umgehen. Jetzt empfinde ich meinen bewussten Lebensstil mit viel Sport, gesunder Ernährung, Rauchverzicht und Körperbewusstsein als Vorteil", berichtet Lena-Rosa. Musik hört sie gerne, trainierte jahrelang Tanzsport in Perchtoldsdorf (NÖ) und geht regelmäßig ins Fitness-Studio.

Univ.-Prof. Dr. Thomas Stulnig, Internist und Stoffwechselexperte am AKH Wien anlässlich eines Symposiums zum Thema, das vor Kurzem in Wien stattfand: „Wir kennen nun auch weitere, seltenere genetische Stoffwechselstörungen, sie werden aber oft übersehen. Dabei kann man sie mittlerweile gut diagnostizieren und behandeln. Je früher eine Therapie einsetzt, umso besser lassen sich Gefäßablagerungen verhindern.

Frühe Herzinfarkte in der Familie als Risikofaktor

Es sind neue Medikamente in Entwicklung und vor der Zulassung, aber wichtig sind Screenings, vor allem, wenn es bereits Vorfälle in der Familie gab, bei Auffälligkeiten Folgeuntersuchungen und Gentests."

Die Daten werden in einem Register unter der Leitung von Univ.-Prof. DDr. Christoph Binder, Österreichische Atherosklerose Gesellschaft, gesammelt und helfen, Leben zu retten! Karin Podolak

Info: www.aas.at (HOME/FH Register, mehr dazu im Kasten rechts oben).

Übermütig: Marie-Violeta tanzt, turnt und lacht viel

PATIENTENREGISTER & SCREENING

„Fass dir ein Herz. Screening und Register für Familiäre Hypercholesterinämie" ist ein Vorsorgeprojekt der **Österreichischen Atherosklerose Gesellschaft** mit dem Ziel, möglichst viele Menschen mit Familiärer Hypercholesterinämie zu identifizieren. Die Datensammlung macht es nicht nur möglich, Betroffenen und ihren Angehörigen eine Behandlung zukommen zu lassen, sondern ermittelt auch Verbreitung, Vor- und Folgeerkrankungen etc., um die Therapieoptionen immer weiter zu verbessern.

Liaise with health politicians

FH Awareness Day 2015: Supported by the Viennese City Counsellor for Health

FH Awareness Week 2016

Supported by 2 Tyrolean health politicians

Austrian Women‘s Run 2018

Supported by the Viennese Mayor and an Austrian MP and former minister

2nd FH Symposium, Nov. 6, 18 Vienna

- Active participation of 8 FH patient testimonials
- Participation of an Austrian health politician
- Presentation of latest Austrian FH Registry data
- Excellent speech on Personalized Medicine

International cooperation

FH Europe: European FH Patient Network

https://fheurope.org/

AUSTRIAN
PLATFORM FOR
PERSONALIZED
MEDICINE

The Austrian Platform for Personalized Medicine

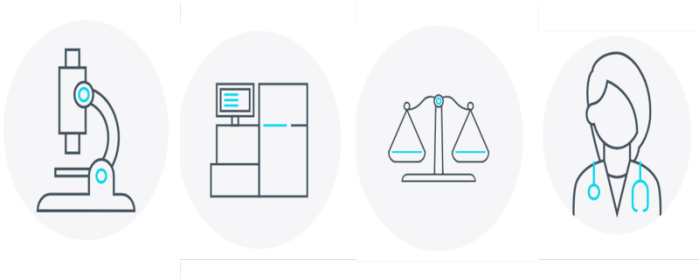
A national networking platform aims to sustainably connect all relevant stakeholders

Implementation of the Objectives

of the Austrian Platform for Personalized Medicine

- **Conference:** one annual conference
  - Inaugural Event and Scientific Symposium (October 2017)
  - 2nd Annual Meeting: ÖPPM – Joining Forces for Personalized Medicine (October 2018)

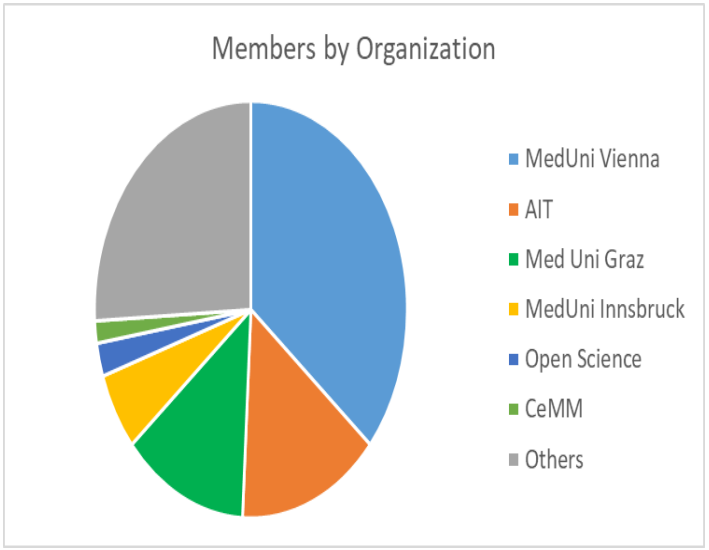
- **Working Groups**
  - Basic and Translational Researc
  - Infrastructure and Technology
  - Society and Ethics
  - Clinical Applications



- **Website**
  - Create and operate a webpage dedicated to PM (launch December 2018)

Members / the Expert Network

of the Austrian Platform for Personalized Medicine



- **116 personal members** (university clinicians, basic scientists, patient advocats, social scientists, non-university researchers, industrial representatives…)
- **12 member organizations**
- The platform is open to all individuals and organizations that would like to contribute to the future of personalized medicine in Austria and beyond.

Organization	N	%
MedUni Vienna	42	36
AIT	17	15
Med Uni Graz	15	13
MedUni Innsbruck	7	6
Open Science	3	3
CeMM	2	2
Others	30	26
Total	116	100

Thank you for your kind attention

Instituto_Nacional de Saúde Doutor Ricardo Jorge

ICPerMed INTERNATIONAL CONSORTIUM

Translational medicine in FH: Ethical Legal and Social Issues

João Lavinha
Human Genetics Department
Instituto Nacional de Saúde Doutor Ricardo Jorge (INSA)
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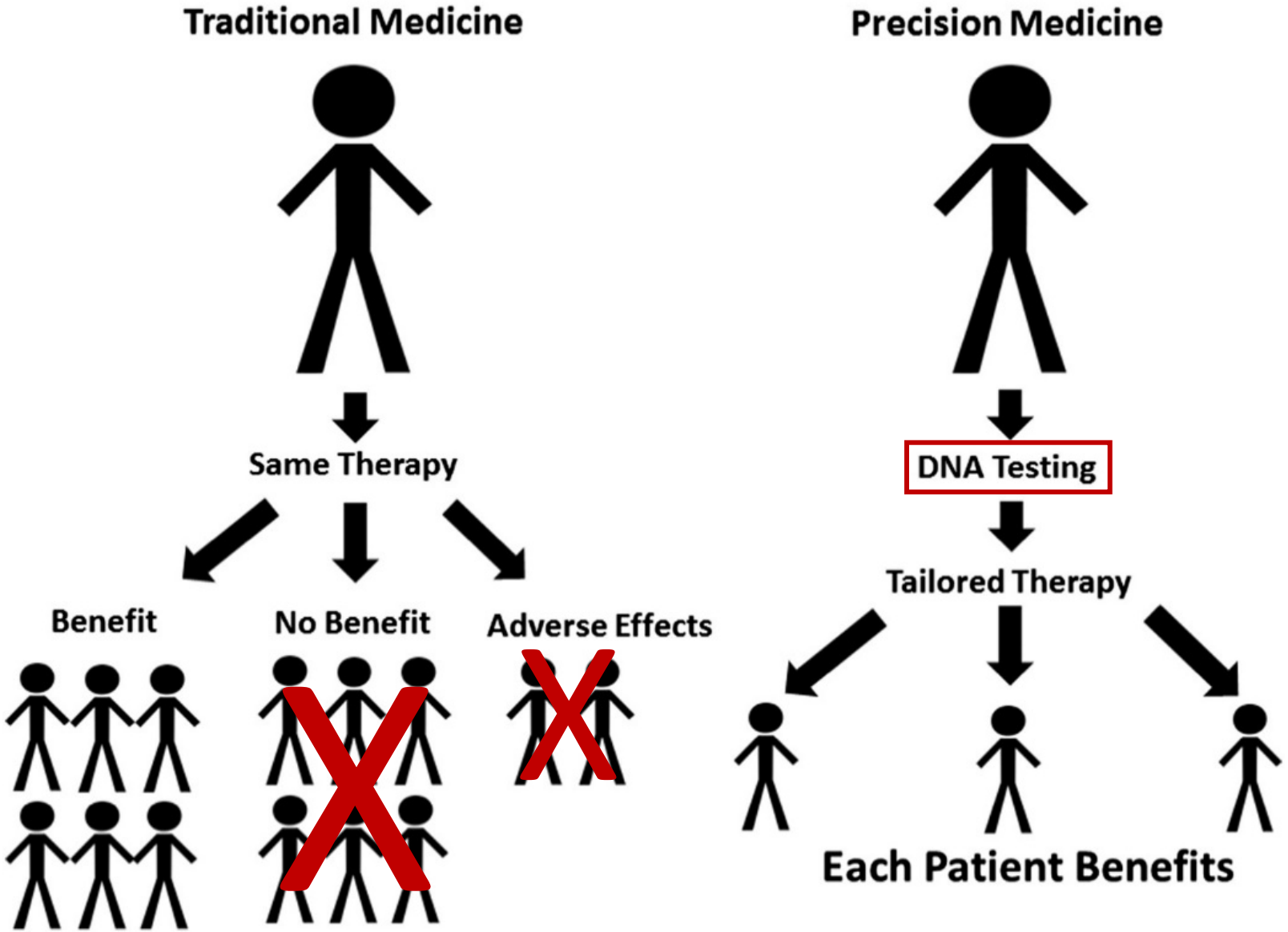
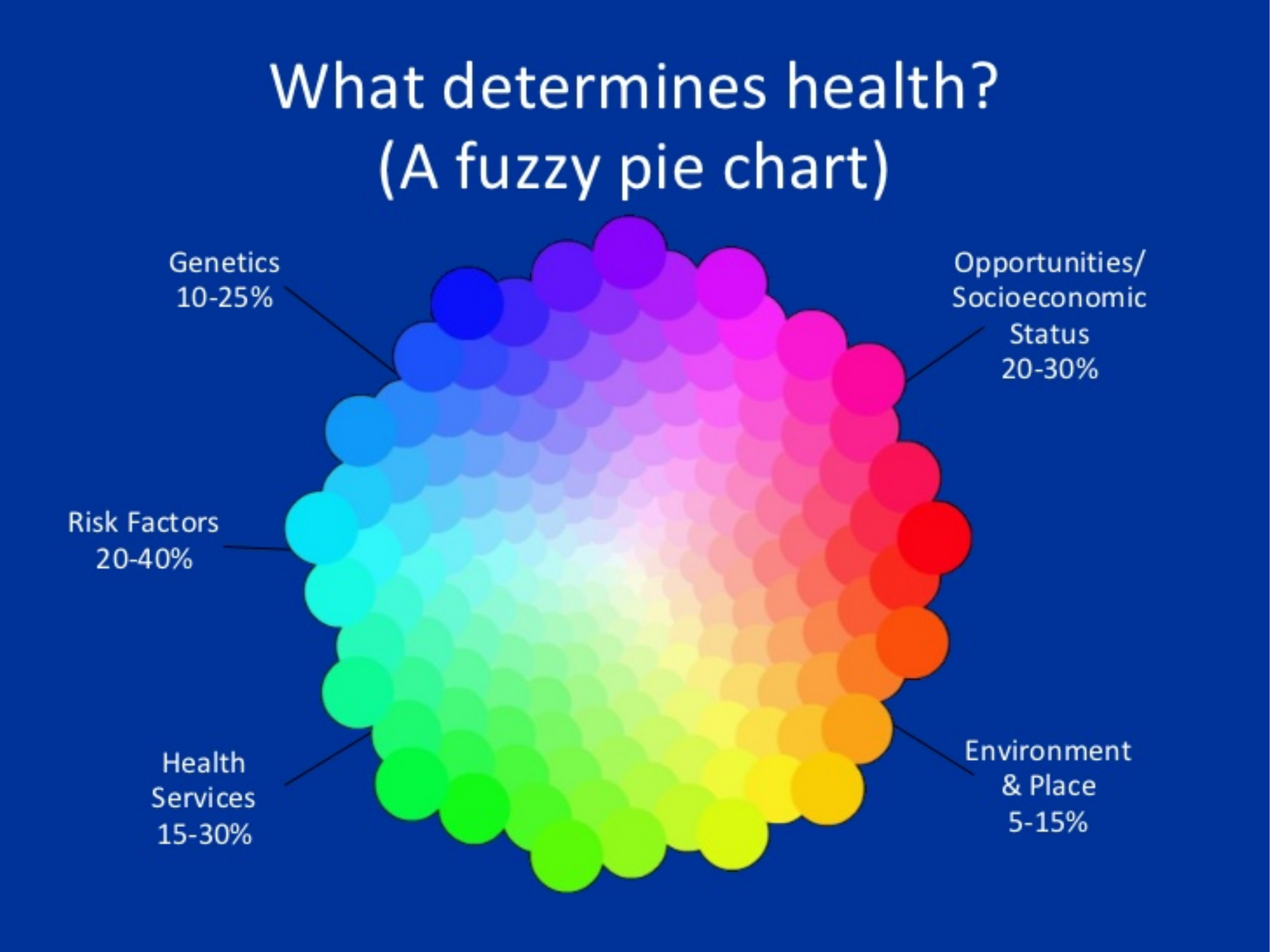
Traditional vs. "Precision" Medicine?



Joyner MJ. Progr Cardiovasc Dis. 2016;58:651-660.



Modifiable and non-modifiable health determinants?

Source:
http://www.slideshare.net/benharrisroxas/what-is-health-impact-assessment

Issues *versus* practice

- Worldwide, less than 1% of FH patients have been identified, although the disease meets the WHO **criteria** for large-scale screening.
- In Portugal,
  - a genetic test (*LDLR, APOB, PCSK9*) is performed in symptomatic FH children and asymptomatic relatives of FH patients: identification and earlier treatment of ~4% of expected cases; to be further improved by NGS of a wider candidate gene panel; interpretation and communication of incidental findings;
  - the affected pathway is determined and characterised: patient stratification for a (more precise) mechanism-based therapy;
  - a patient registry (as part of ongoing international initiatives) is being set up.

Lessons learned

- Beyond the individual's genetic make-up, "the protection or restoration of individual health results from structural transformations affecting the population as a whole" (Chowkwanyun et al. NEJM. 2018;379:1398-1400):
  - Life styles (social class, ethnic background, gender and sexual identity), physical environment.
  - Dyslipidaemia control, including in FH, is particularly susceptible to the structural factors above.
  - Genomics: a tool in an expanding arsenal not to be used in isolation.
  - Epigenetics as part of gene x environment interactions.
- Although genetic services and screening programs aim to improve the health of the population, there is growing concern that the increasing number of genetic tests becoming available at lower costs could compromise the viability of the health care system.
  - Clinical utility assessment mandatory before the test is reimbursed.
- In spite of the Portuguese NHS being universal, general and virtually free at the point of care, many health inequities remain to be solved by improving other policies (food, city planning, housing, education,…).