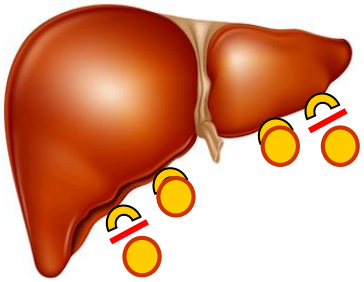
Ipercolesterolemia familiare: dai registri alla pratica clinica

Manuela Casula

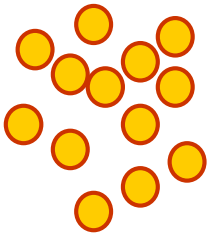
Familial Hypercholesterolemia

Mutations

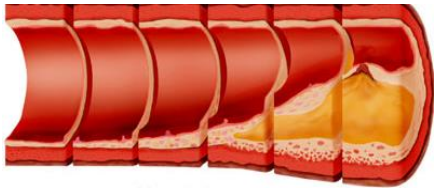
Liver with less functional LDL receptors



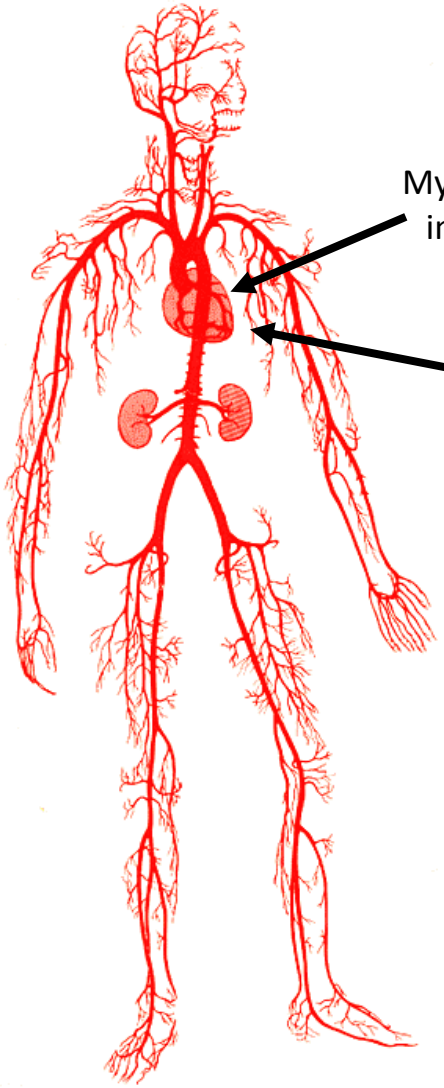
Elevated LDL cholesterol



Atherosclerosis

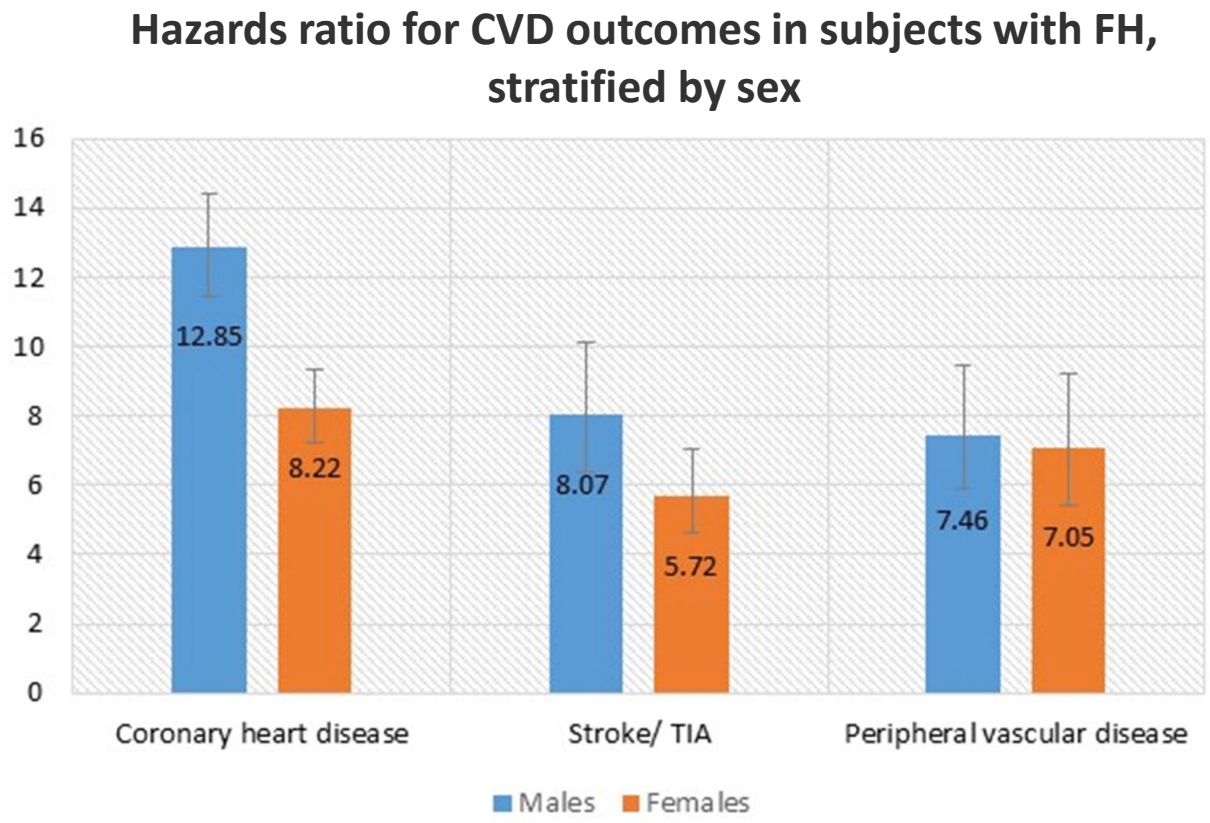


Coronary heart disease



Familial hypercholesterolaemia: A global call to arms

Burden of disease

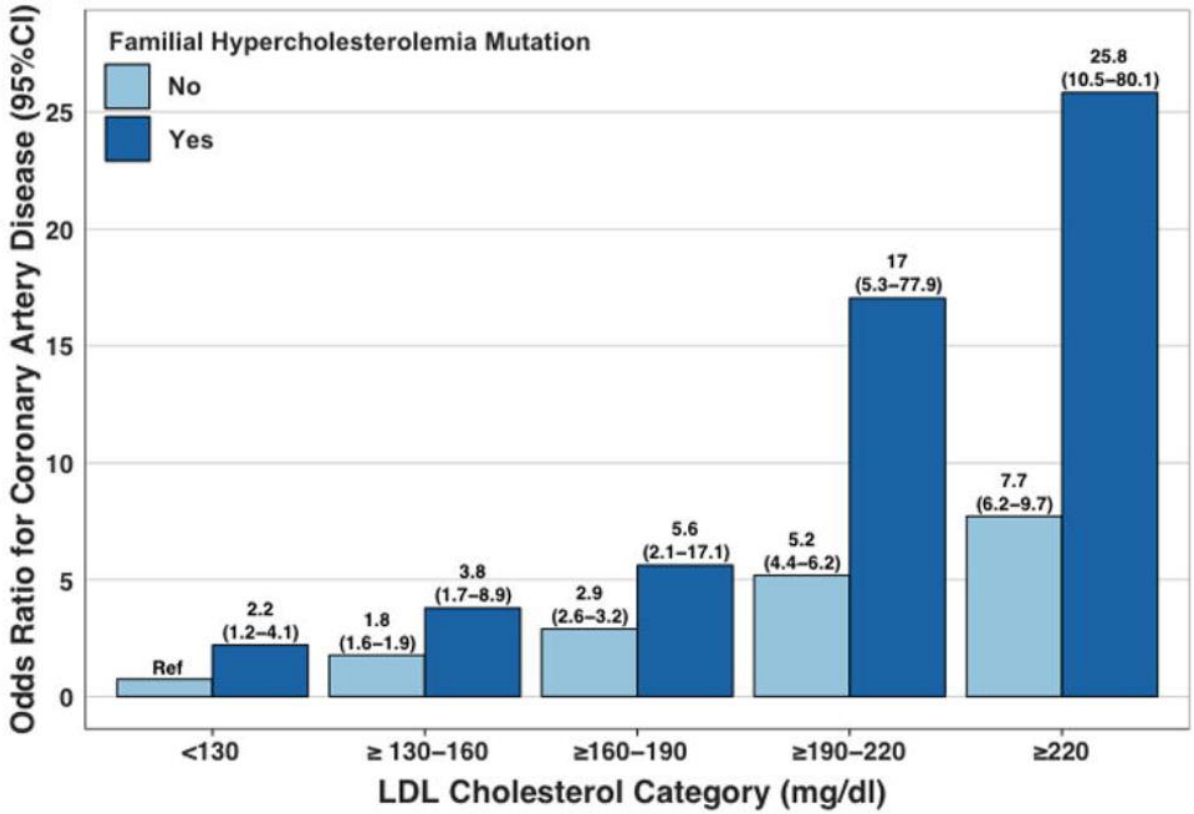


Iyen B, et al. Atherosclerosis 2019;287:8-15

Familial hypercholesterolaemia: A global call to arms

Burden of disease

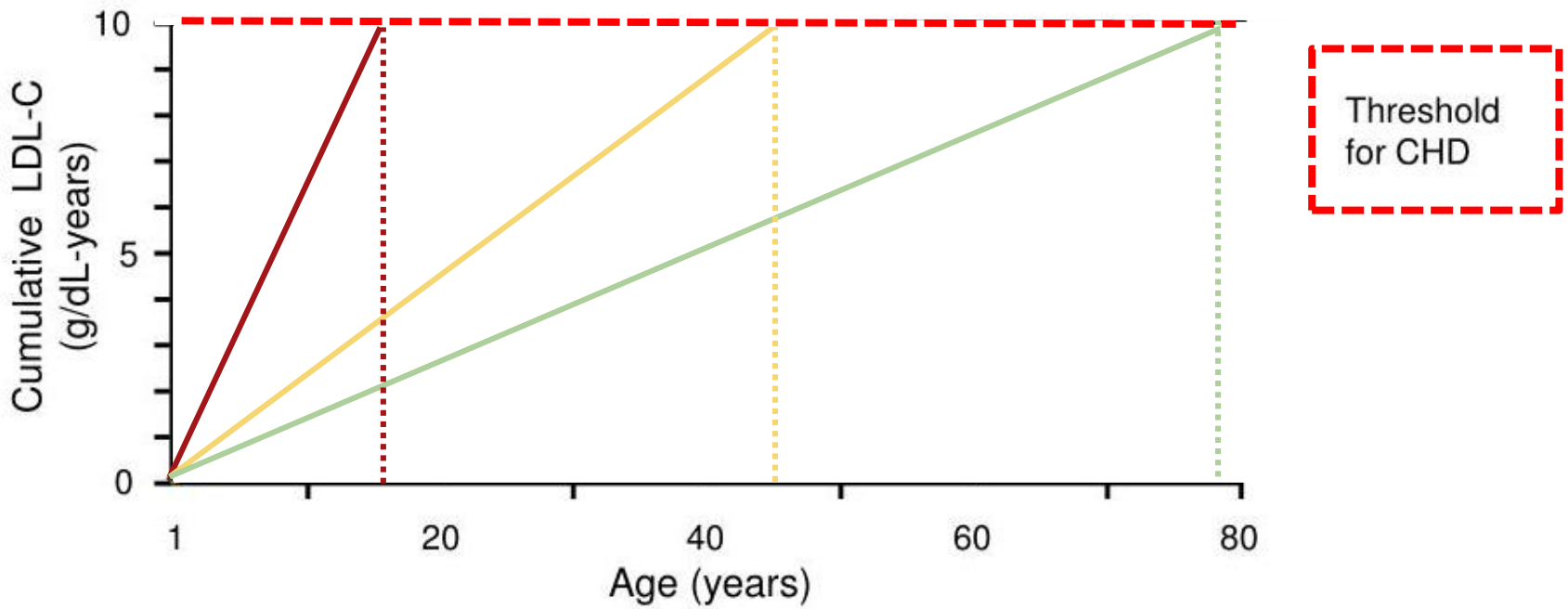
Impact of FH mutation status on CAD



Khera et al. J Am Coll Cardiol. 2016 Jun 7; 67(22): 2578–2589

Burden of disease

Cumulative exposure to LDL-C from birth and threshold for CHD



Adapted from Horton JD, et al. J Lipid Res 2009; 50(Suppl): S172-S177

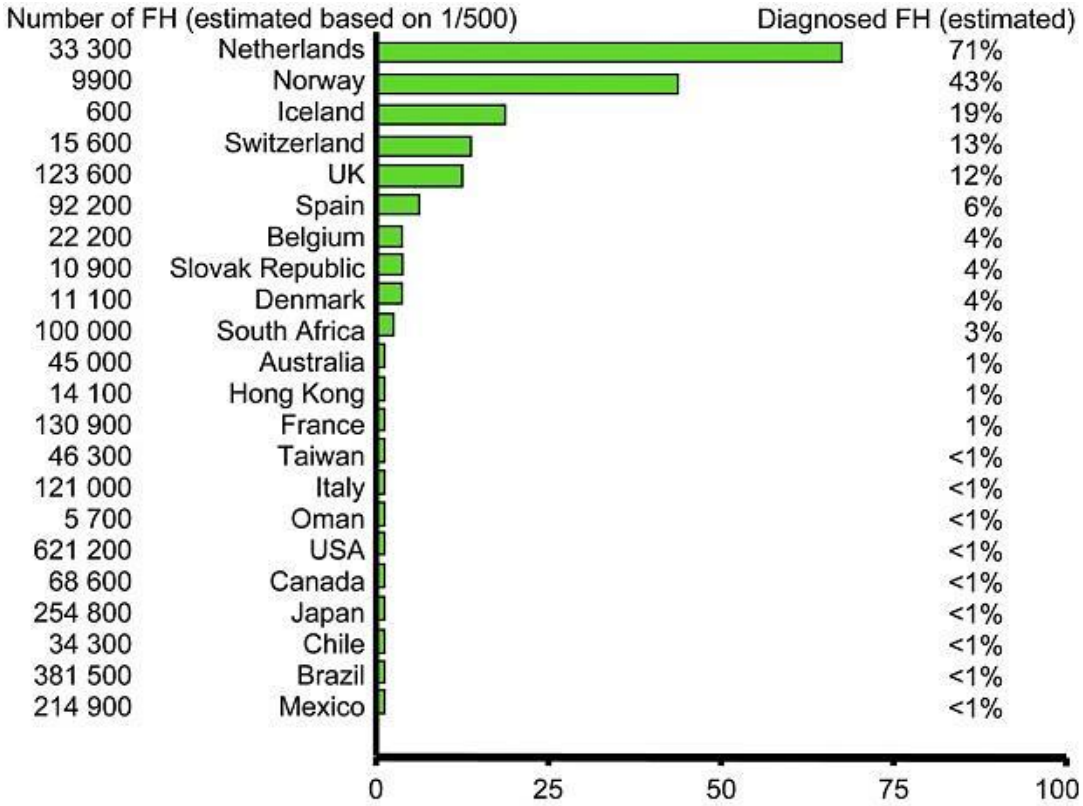
Familial hypercholesterolaemia: A global call to arms

Cumulative incidence of all-cause mortality and major adverse cardiovascular events

Burden of disease

Underdiagnosed

Estimated % of Individuals Diagnosed with FH



EAS consensus statement. Nordestgaard et al. Eur Heart J 2013; 34: 3478-90

Familial hypercholesterolaemia: A global call to arms

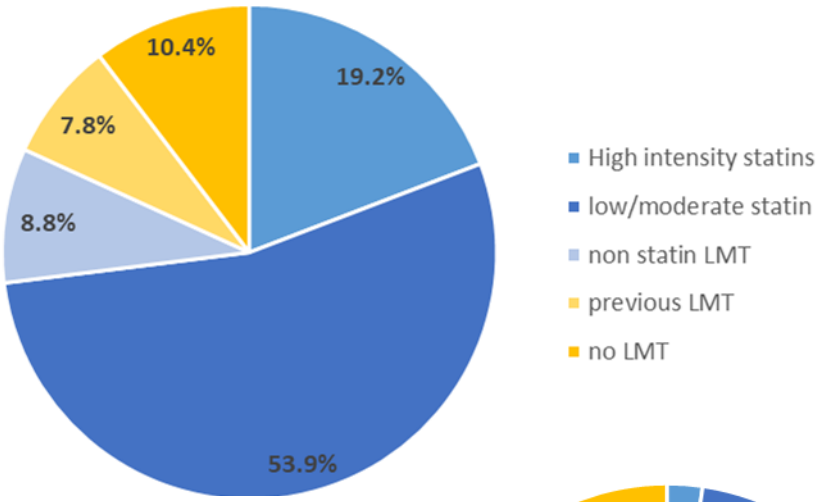
Cumulative incidence of all-cause mortality and major adverse cardiovascular events

Burden of disease

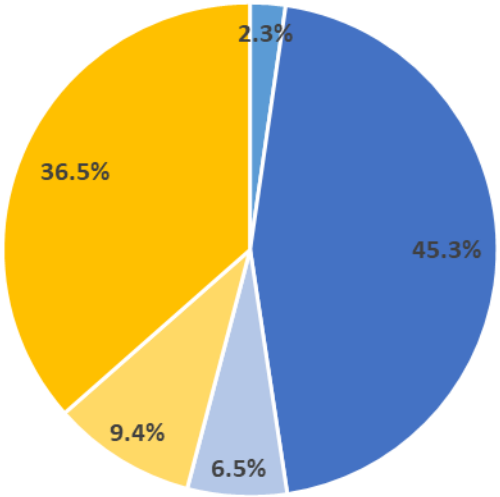
Underdiagnosed

Undertreated

FH-D



FH-S



Teramoto T et al. J Atheroscler Thromb. 2018 Jul 1; 25(7): 580–592

Familial hypercholesterolaemia: A global call to arms

Burden of disease

Underdiagnosed

Undertreated

- Diagnosis screening
- Registries
- Research
- Awareness/education
- Policies
- Therapy

Vallejo-Vaz, et al. Atherosclerosis. 2015 Nov;243(1):257-9

Familial hypercholesterolaemia: A global call to arms

Burden of disease

Underdiagnosed

Undertreated

- Diagnosis screening
- Registries
- Research
- Awareness/education
- Policies
- Therapy

Vallejo-Vaz, et al. Atherosclerosis. 2015 Nov;243(1):257-9

FH registries

Mata et al. Lipids in Health and Disease 2011, 10:94
http://www.lipidworld.com/content/10/1/94

LIPIDS IN HEALTH AND DISEASE

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n of
anish Familial
Cohort Study

vidio Muñiz[5],
Mar Piedecausa[9],
Mata[2*]

AHJ
American Heart Journal

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HORMONES 2017, 16(3):306-312

Research pap

An insight in
in Greece: ra
Hypercholest

Christos V. Rizos,[1] V
Genovefa Kolovou
Ioannis Skoumas,[1]

Atherosclerosis 277 (2018) 413–418

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Evaluation of the performance of
Italian FH population: The LIPIGE

Manuela Casula[a,b], Elena Olmastroni[a,b], Ang
of the LIPIGEN Group[1]

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[c] Center for the Study of Atherosclerosis, E. Bassini Hospital, Cinisello Balsa
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frontiers in Physiology

REVIEW
published: 20 March 2019
doi: 10.3389/fphys.2019.00280

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Current Status of Familial Hypercholesterolemia in China: A Need for Patient FH Registry Systems

Peipei Chen, Xi Chen and Shuyang Zhang*

FH registries: Canada FH registry

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HF Canada
Hypercholestérolémie Familiale

FH Canada
Familial Hypercholesterolemia

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FH Canada **Registry**

The purpose of this initiative is to create a registry of subjects with FH across Canada.

FH registries: CASCADE FH

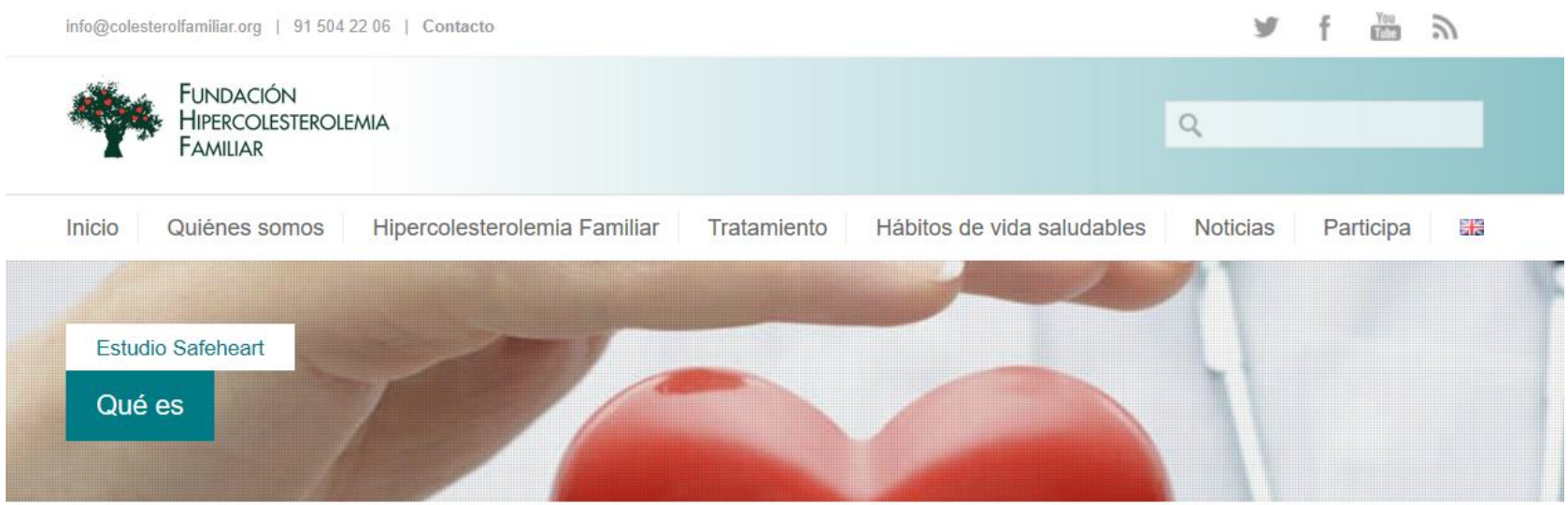
The Familial Hypercholesterolemia Patient Registry

The **CAscade SCreening for Awareness and DEtection of Familial Hypercholesterolemia (CASCADE FH) Registry** is a national, multicenter initiative to identify US FH patients, track their treatment, and clinical and patient-reported outcomes over time.

Enrollment framework:

1) Clinic enrollment
2) Self-enrollment
3) EHR identification coupled with patient contact and enrollment

FH registries: SAFEHEART Study



The **SpAnish Familial HypErcHolEsterolaemiA CohoRt STudy (SAFEHEART)** is an open, multicenter, long-term prospective cohort study in a well-defined FH population, conducted in outpatient lipid clinics in Spain.

Inclusion criteria are:

1) index cases with genetic diagnosis of FH,
2) relatives over 15 years old with genetic diagnosis of FH,
3) *relatives over 15 years old without a genetic diagnosis of FH (control group).*

FH registries: LIPIGEN study

The **LIpid TransPort Disorders Italian GEnetic Network (LIPIGEN) - Registro delle Dislipidemie Familiari in Italia** is an observational, multicentric, retrospective and prospective study, aimed at creating an Italian Database of Familial Hypercholesterolemia.

FH patients are included, identified with clinical evaluation **<u>and/or</u>** genetic polymorphism

FH registries

ELSEVIER

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Atherosclerosis Supplements 22 (2016) 1–32

ATHEROSCLEROSIS SUPPLEMENTS

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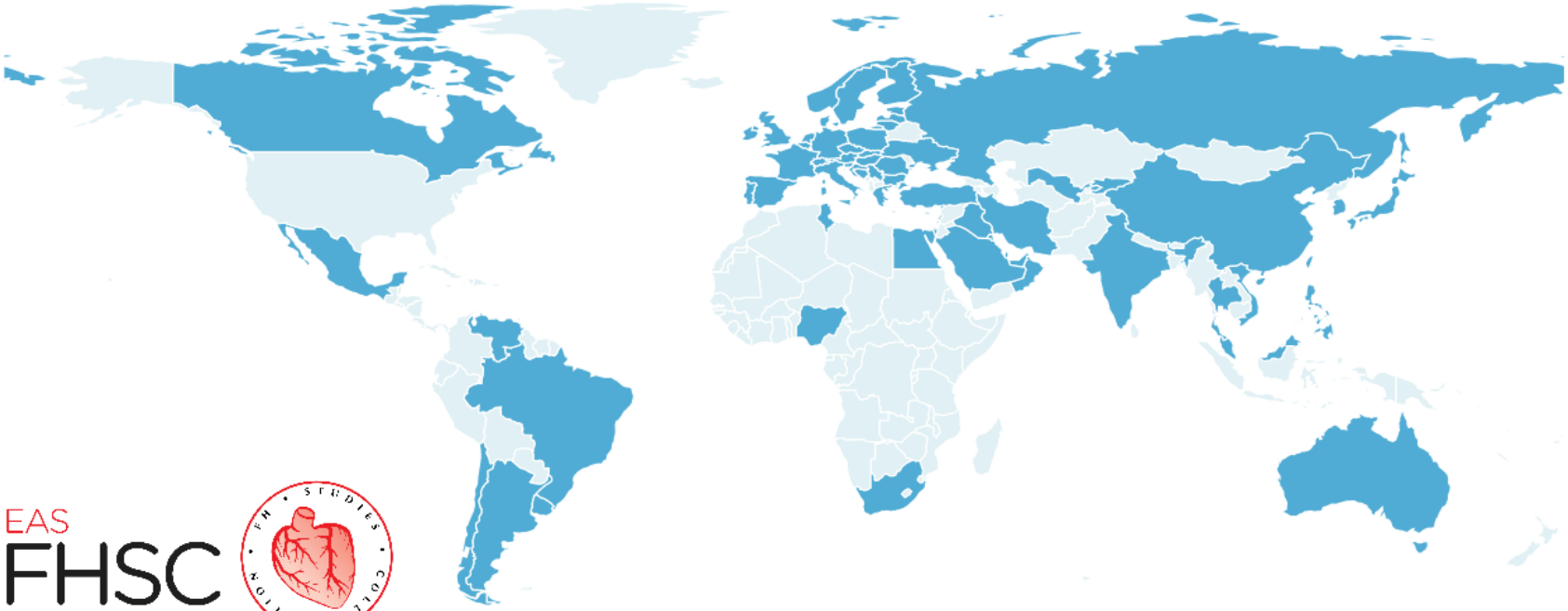
Pooling and expanding registries of familial hypercholesterolaemia to assess gaps in care and improve disease management and outcomes: Rationale and design of the global EAS Familial Hypercholesterolaemia Studies Collaboration

The EAS Familial Hypercholesterolaemia Studies Collaboration, Antonio J. Vallejo-Vaz [a,*], Asif Akram [b,u], Sreenivasa Rao Kondapally Seshasai [c], Della Cole [c], Gerald F. Watts [d], G. Kees Hovingh [e], John J.P. Kastelein [e], Pedro Mata [f], Frederick J. Raal [g], Raul D. Santos [h], Handrean Soran [i], Tomas Freiberger [j,k], Marianne Abifadel [l], Carlos A. Aguilar-Salinas [m], Fahad Alnouri [n], Rodrigo Alonso [o], Khalid Al-Rasadi [p], Maciej Banach [q], Martin P. Bogsrud [r], Mafalda Bourbon [s], Eric Bruckert [t], Josip Car [b,u], Richard Ceska [v], Pablo Corral [w], Olivier Descamps [x], Hans Dieplinger [y], Can T. Do [z], Ronen Durst [aa], Marat V. Ezhov [ab], Zlatko Fras [ac,ad], Dan Gaita [ae], Isabel M. Gaspar [af], Jaques Genest [ag], Mariko Harada-Shiba [ah], Lixin Jiang [ai], Meral Kayikcioglu [aj], Carolyn S.P. Lam [ak], Gustavs Latkovskis [al], Ulrich Laufs [am], Evangelos Liberopoulos [an], Jie Lin [ao], Nan Lin [a], Vincent Maher [ap], Nelson Majano [aq], A. David Marais [ar], Winfried März [as], Erkin Mirrakhimov [at], André R. Miserez [au,av], Olena Mitchenko [aw], Hapizah Nawawi [ax], Lennart Nilsson [ay], Børge G. Nordestgaard [az], György Paragh [ba], Zaneta Petrulioniene [bb], Belma Pojskic [bc], Željko Reiner [bd], Amirhossein Sahebkar [be], Lourdes E. Santos [bf], Heribert Schunkert [bg], Abdullah Shehab [bh], M. Naceur Slimane [bi], Mario Stoll [bj], Ta-Chen Su [bk], Andrey Susekov [bl], Myra Tilney [bm], Brian Tomlinson [bn], Alexandros D. Tselepis [bo], Branislav Vohnout [bp], Elisabeth Widén [bq], Shizuya Yamashita [br], Alberico L. Catapano [bs], Kausik K. Ray [a]

FH studies collaboration



EAS FHSC

EAS FH Studies Collaboration - a global call to action

"The mission of the EAS-FHSC is to empower the medical & global community to seek changes in their respective countries or organizations regarding how FH is detected and managed, with a view to promoting early diagnosis and more effective treatment of this condition. Through international collaboration of stakeholders EAS FHSC aims to generate large scale robust data on how FH is detected, managed and the clinical consequences of current practice on outcomes."

FH registries

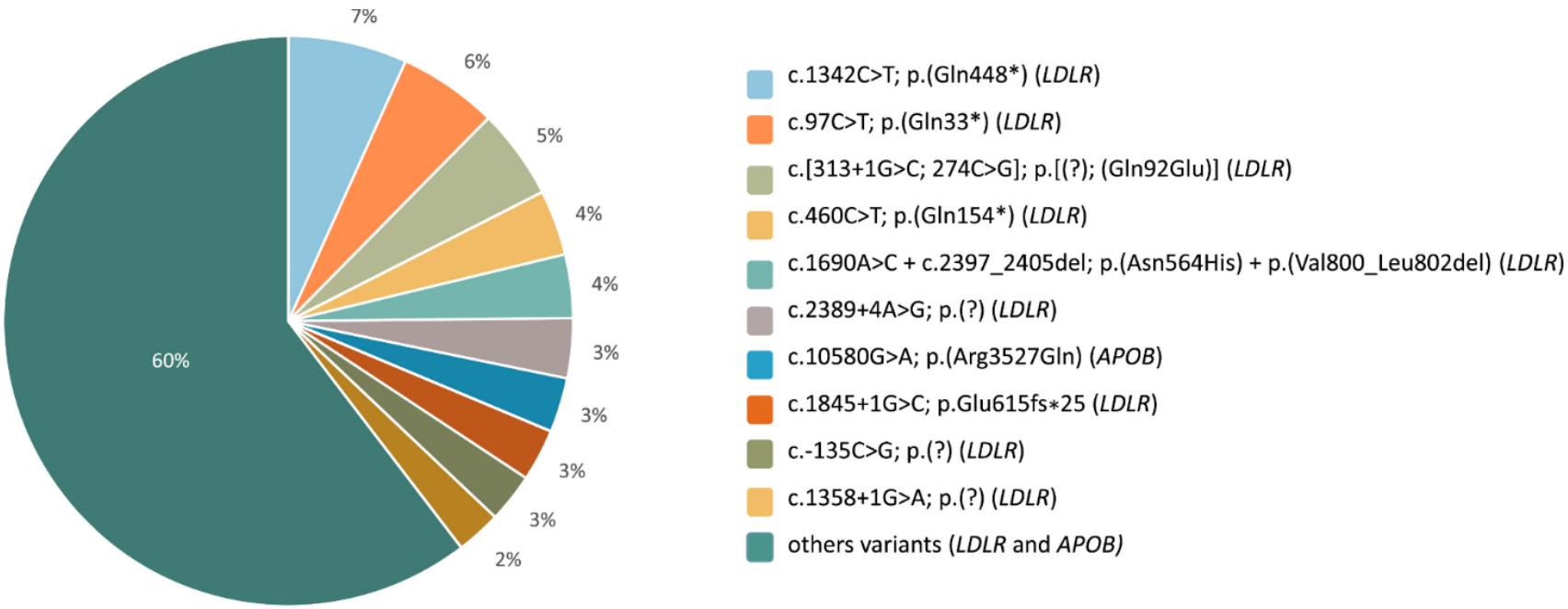
Discovery of new monogenic/polygenic causes of FH phenotype

FH registries

Mutational analysis and genotype-phenotype relation in familial hypercholesterolemia: The SAFEHEART registry

Bourbon M, et al. Atherosclerosis. 2017 Jul;262:8-13

2938 individuals with **genetic** diagnosis of FH belonging to 775 families



FH registries

Mutational analysis and genotype-phenotype relation in familial hypercholesterolemia: The SAFEHEART registry

Bourbon M, et al. Atherosclerosis. 2017 Jul;262:8-13

194 variants have been detected in this study, 24 of them were never described before.

Description and overall *in silico* classification of the 24 new alterations found in this study.

cDNA	Protein	Gene	Alteration type	Overall *in silico*	Allele type - predicted	ACMG
c.2853G > A	p.(=)	APOB	PS (synonymous)	?	NPD	VUS
c.8148C > T	p.(=)	APOB	PS (synonymous)	?	NPD	VUS
c.10588G > A	p.(Val3530Met)	APOB	PS (missense)	?	Defective	VUS
c.-228G > C	p.(?)	LDLR	PS (regulatory)	NA	NPD	VUS
c.91_104del	p.(Glu31Argfs*16)	LDLR	Del (14 nucleotides)	?	Null	Pathogenic
c.131G > T	p.(Trp44Leu)	LDLR	PS (missense)	Pathogenic	Defective	VUS
c.191-?_2583+?del	p.(?)	LDLR	Del (large rear)	NA	Null	Likely pathogenic
c.362_376del	p.(Cys121_Gln125del)	LDLR	Del (in frame)	Pathogenic	Defective	Likely pathogenic
c.440_450dup	p.(Ala151Profs*59)	LDLR	Ins (11 nucleotides)	?	Null	Pathogenic
c.479G > T	p.(Cys160Phe)	LDLR	PS (missense)	Pathogenic	Defective	Likely pathogenic
c.706T > A	p.(Cys236Ser)	LDLR	PS (missense)	Pathogenic	Defective	VUS
c.890A > C	p.(Asn297Thr)	LDLR	PS (missense)	Pathogenic	Defective	VUS
c.890A > G	p.(Asn297Ser)	LDLR	PS (missense)	Pathogenic	Defective	VUS
c.910G > C	p.(Asp304His)	LDLR	PS (missense)	Pathogenic	Defective	Likely pathogenic
c.987C > A	p.(Cys329*)	LDLR	PS(missense)	?	Null	Pathogenic
c.1013G > T	p.(Cys338Phe)	LDLR	PS (missense)	Pathogenic	Defective	Likely pathogenic
c.1061-?_1586+?del	p.(?)	LDLR	Del (large rear)	NA	Null	Likely pathogenic
c.1359-?_1586+?del	p.(?)	LDLR	Del (large rear)	NA	Null	Likely pathogenic
c.1359-27T > G	p.(?)	LDLR	PS (splicing)	?	NPD	VUS
c.1749C > G	p.(His583Gln)	LDLR	PS (missense)	Pathogenic	Defective	Likely pathogenic
c.1981C > A	p.(Pro661Thr)	LDLR	PS (missense)	Pathogenic	Defective	VUS
c.2011del	p.(Thr671Profs*2)	LDLR	Del (1 nucleotides)	?	Null	Pathogenic
c.2054C > A	p.(Pro685Gln)	LDLR	PS (missense)	Pathogenic	Defective	Likely pathogenic
c.2270del	p.(Pro757Leufs*8)	LDLR	Del (1 nucleotides)	?	Null	Pathogenic

Allele type - predicted means that the allele type has been predicted by the analysis of the nature of the alteration or using the results of the *in silico* analysis. PS, point mutation; Del, deletion; large rear, large rearrangements; Ins, insertion.
Overall *in silico* as described in the Materials and methods section; ?, the *in silico* analysis was not conclusive; NA, not applicable; NPD, not possible to determine ACMG, classification by the American College of Medical Genetics and genomics.

FH registries

Spectrum of mutations in Italian patients with familial hypercholesterolemia: New results from the LIPIGEN study

Pirillo A, et al. Atherosclerosis. 2017 Oct;29:17-24

213 variants were detected in 1076 subjects, 90% of them had a pathogenic or likely pathogenic variants.

More than 94% of patients carried pathogenic variants in *LDLR* gene, 27 of which were novel.

New *LDLR* gene variants.

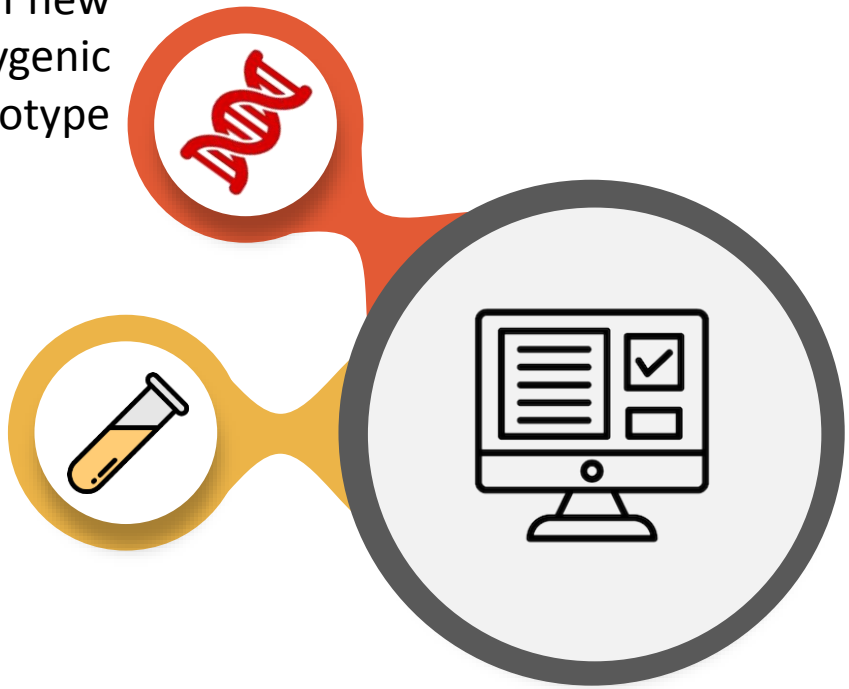
Gene variant (c.DNA)	Type of variant	Clinical significance	Protein change
c.-97G>A	Promoter	Reduced transcription?	
c.3G>A	Aa change	Pathogenic	p.(Met1Ile)
c.38_58del21	Deletion	Pathogenic?	p.(Ala13_Ala19del)
c.68-?_190+?dup	Exon 2 duplication	Pathogenic	p.(Gly24_Leu64dup)
c.94T>C	Aa change	Pathogenic	p.(Phe32Leu)
c.191-?_2311+?dup	Exons 3–15 duplication	Pathogenic	p.[Ala771Val; Ser65_Ala771dup]
c.246delC	Deletion	Pathogenic	p.(Cys82*)
c.313+4_313+16del13	Affects donor splice site	Pathogenic (new donor splice site in exon 3)	p.(Arg88Serfs*25)
c.314-?_2583+?del	Exons 4–18 deletion	Pathogenic	p.0
c.316_328delCCCAAGACGTGCT	Deletion	Pathogenic	p.(Lys107Argfs*95)
c.363C>A	Nonsense	Pathogenic	p.(Cys121*)
c.620_626delGCGAGTG	Deletion	Pathogenic	p.(Gly207Alafs*56)
c.641G>A	Aa change	Pathogenic	p.(Trp214*)
C.688A>G	Aa change	Unlikely pathogenic	p.(Asn230Asp)
c.698T>C	Aa change	Unlikely pathogenic	p.(Val233Ala)
c.906C>A	Aa change	Pathogenic	p.(Cys302*)
c.920A>C	Aa change	Pathogenic	p.(Asp307Ala)
c.926C>A	Aa change	Pathogenic	p.(Pro309His)
c.1037delT	Deletion	Pathogenic	p.(Leu346Argfs*24)
c.1061-1G>T	Acceptor splice site broken	Pathogenic (skipping Exon 8)	
c.1171delG	Deletion	Pathogenic	p.(Ala391Profs*22)
c.1413_1414delAGinsGGACAT	Insertion/deletion	Pathogenic	p.(Gln474Hisfs*63)
c.1470G>T	Aa change	Pathogenic	p.(Trp490Cys)
c.1491delT	Deletion	Pathogenic	p.(Val498Serfs*9)
c.1498delG	Deletion	Pathogenic	p.(Val500Leufs*7)
c.1587-?_2583+?del	Exons 11–18 deletion	Pathogenic	p.0
c.1686G>T	Aa change	Pathogenic	p.(Trp562Cys)
c.1943_1944delCCinsG	Deletion	Pathogenic	p.(Ser48Cysfs*17)
c.2120A>C	Aa change	Pathogenic	p.(Asp707Ala)
c.2257C>G	Aa change	Unlikely pathogenic	p.(Pro753Ala)
c.2311_2311+15del16	Donor splice site broken	Pathogenic	
c.2299A>G	Aa change	Possibly pathogenic	p.(Met767Val)

In silico analysis of missense mutations was performed using PolyPhen-2 HumDiv and Hum Var (http://genetics.bwh.harvard.edu/pph2/), SIFT Human Protein (http://sift.jcvi.org/) and Mutation Taster (www.mutationtaster.org/). The potential effect of an intronic variant on pre-mRNA splicing was assessed by Human Splicing Finder (http://www.umd.be/HSF3/HSF.html), NetGene2 (http://www.cbs.dtu.dk/sevices/NetGene2/), BDGP Splice Site prediction (http://www.fruitfly.org/seq_tools/splice.html), Splice Port (http://spliceport.cbcb.umd.edu/) and Splice Site Score Calculation (http://rulai.cshl.edu/new_alt_exon_db2/HTML/score.html).

FH registries

Discovery of new monogenic/polygenic causes of FH phenotype

Correlation of genotype with phenotype



FH registries

Mutational analysis and genotype-phenotype relation in familial hypercholesterolemia: The SAFEHEART registry

Bourbon M, et al. Atherosclerosis. 2017 Jul;262:8-13

Clinical and biochemical characteristics of the 2643 adults patients by allele type

	Null	n	Defective	n	p null vs. defective
Age (yr)	45.9 ± 15.8	911	45.8 ± 15.7	1259	0.830
BMI (kg/m^2)	26.4 ± 4.7	911	26.4 ± 4.9	1257	0.626
Td Xant (%)	16.6%	151	10.7%	150	**<0.001**
premature ASCVD (%)	10.2%	93	9.1%	114	0.114
TC	327.6 ± 69.4	911	320.1 ± 66.9	1259	**0.007**
LDL-C	264.1 ± 69.0	911	253.9 ± 68.9	1259	**<0.001**
HDL-C	49.2 ± 12.3	911	50.4 ± 12.7	1259	0.052
TG*	81.0 (52.0)	911	84.0 (54.0)	1259	0.146
Lp(a)*	24.0 (48.7)	865	21.0 (43.8)	1166	0.343
apoB	163.6 ± 43.6	871	153.2 ± 42.6	1181	**<0.001**

FH registries

Homozygous Familial Hypercholesterolemia in Spain. Prevalence and Phenotype–Genotype Relationship.

Sánchez-Hernández RM, et al. Circ Cardiovasc Genet. 2016 Dec;9(6):504-510

Characteristics of True Homozygotes, Compound Heterozygotes, and Double Heterozygotes

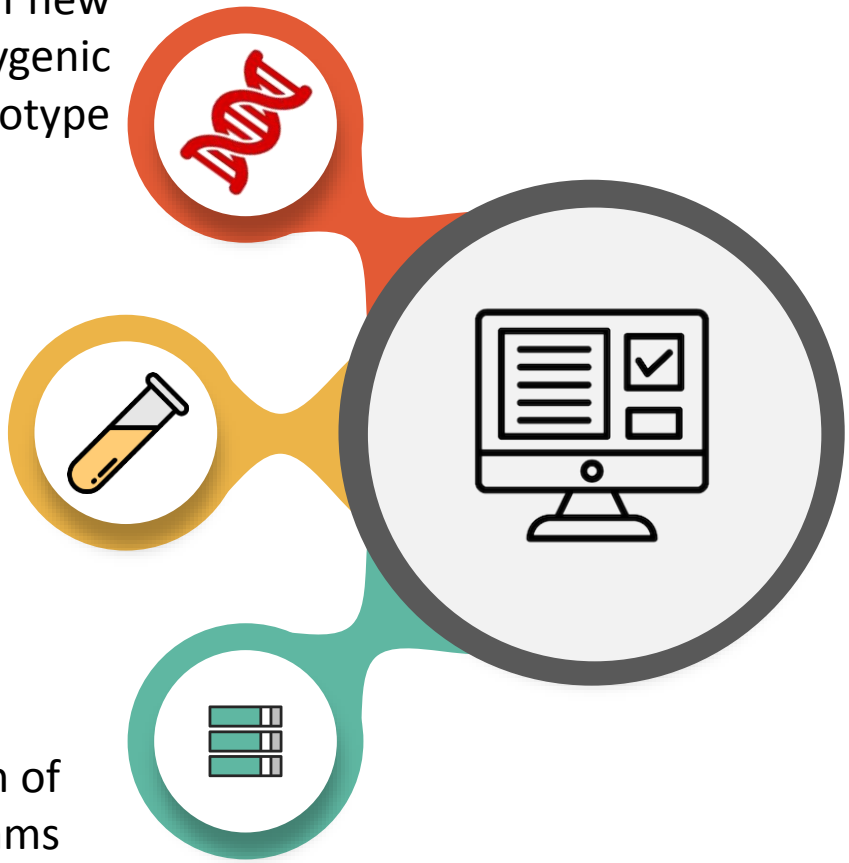
	True Homozygotes (LDLR)	Compound Heterozygotes (LDLR)	Double Heterozygotes	P
N	41	45	3+2	
Age, y	36.8 (18.4)	37.9 (18.56)	52.5 (28.2)	NS
Male sex, %	73.3	51.7	25	0.065
TC, mg/dL	692 (262)	465 (279–950)	370 (25.54)	0.005
LDL-C, mg/dL	625 (271.5)	397 (197–890)	304 (37)	0.008
HDL-C, mg/dL	43 (14)	48.7 (15)	48 (7)	NS
Triglycerides, mg/dL	100 (42)	105 (26–514)	65 (17)	NS
ASCVD, %	46.4	25	25	NS
Age of ASCVD	31.7 (17)	34.3 (17.4)	43	NS

FH registries

Discovery of new monogenic/polygenic causes of FH phenotype

Correlation of genotype with phenotype

Local adaptation of diagnostic algorithms



FH registries

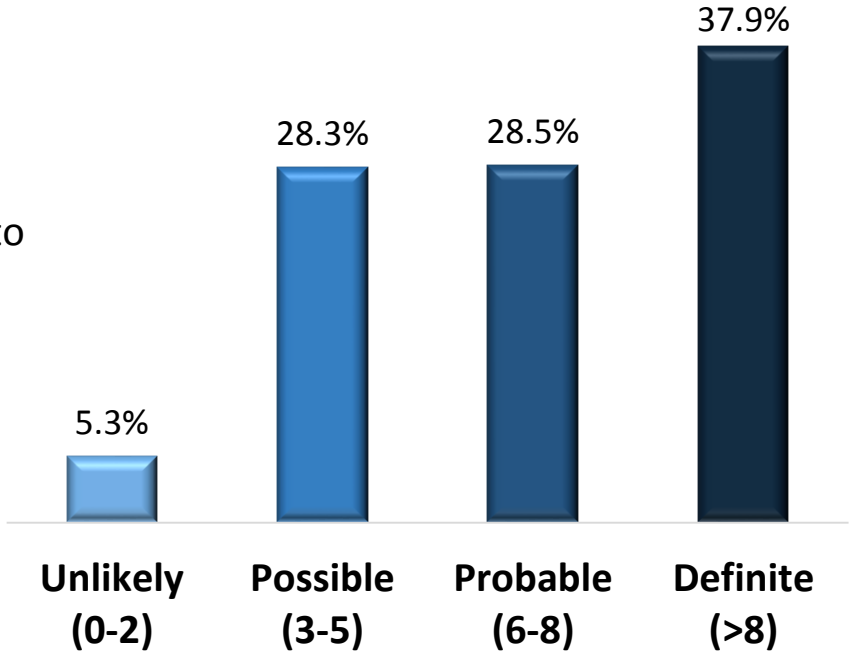
Evaluation of the performance of Dutch Lipid Clinic Network score in an Italian FH population: The LIPIGEN study.

Casula M, et al. Atherosclerosis. 2018 Oct;277:413-418

DLCN score applied on 1377 adults with genetic diagnosis of FH

- 43% of patients with at least 1 missing data
- Possible FH from 61% with untreated LDL-C levels to 82% with estimated pre-treatment values.

	OR	95% CI	
Tendon xanthoma	2.47	1.41	4.32
Premature CHD	1.24	0.79	1.94
LDL-C >180 mg/dL since age <18 yy	1.83	1.26	2.66
First-degree relative with hyperchol.	2.33	1.49	3.64
First-degree relative with xanthoma	5.51	2.28	13.31
Child(ren) <18 yy with high LDL-C	1.82	1.21	2.74
251 ≤ LDL-C ≤ 325 mg/dL	3.84	2.03	7.25
LDL-C >325 mg/dL	15.5	7.12	33.75



FH registries

Discovery of new monogenic/polygenic causes of FH phenotype

Study of treatment compliance and response

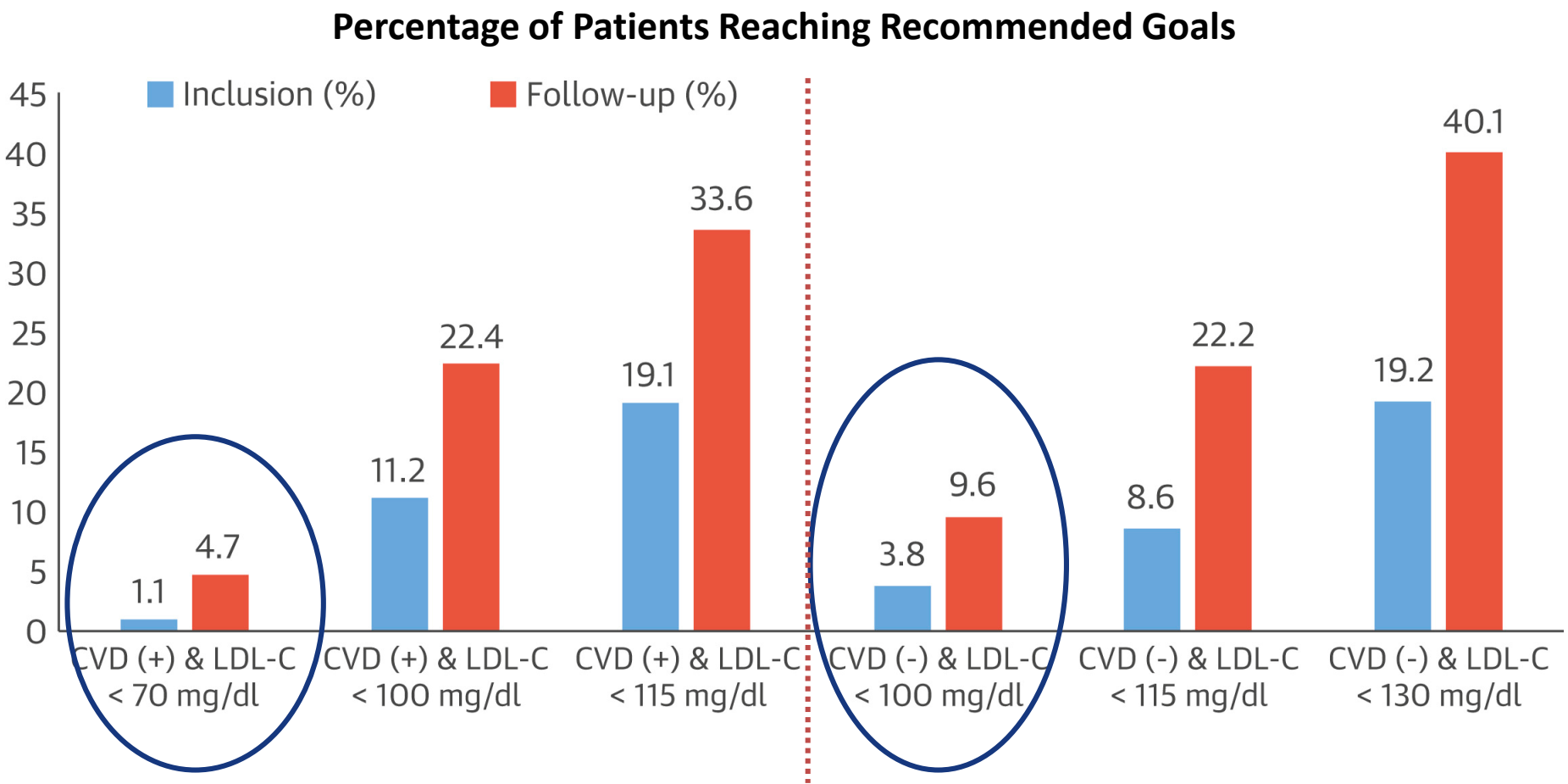
Correlation of genotype with phenotype

Local adaptation of diagnostic algorithms

FH registries

Attainment of LDL-Cholesterol Treatment Goals in Patients With Familial Hypercholesterolemia: 5-Year SAFEHEART Registry Follow-Up

Perez de Isla, et al. J Am Coll Cardiol. 2016 Mar 22;67(11):1278-85



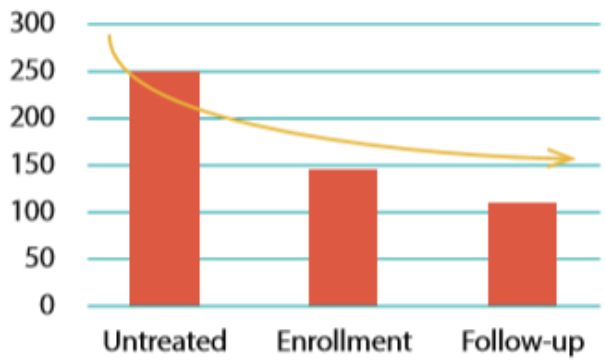
FH registries

Goal achievement and cardiovascular outcomes among adults with familial hypercholesterolemia: CASCADE FH® Registry

Majority of FH individuals did NOT meet guideline-based LDL cholesterol targets despite $^{2}/_{3}$ of patients taking two or more lipid-lowering medications

Adults under specialty FH care were able to further lower LDL-C, but not far enough

Mean LDL-C Results Over Time



Individuals who had prior cardiovascular disease were more likely to meet targets because they were on 3-6 lipid-lowering therapies including PCSK9 inhibitors or were receiving lipoprotein apheresis

did NOT achieve LDL-C <100 mg/dL

did NOT achieve LDL-C <70 mg/dL

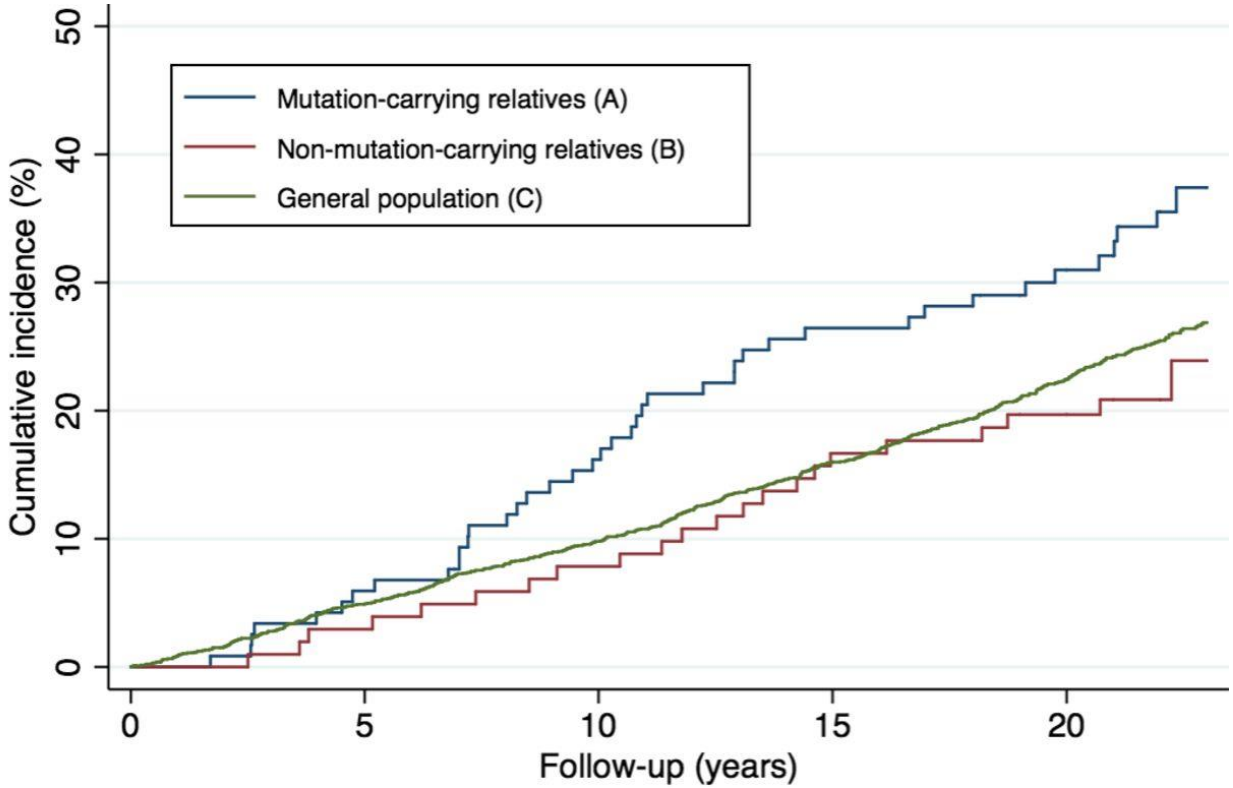
FH registries

FH registries

Long-Term Cardiovascular Risk in Heterozygous Familial Hypercholesterolemia Relatives Identified by Cascade Screening

Aalbæk Kjærgaard K, et al. J Am Heart Assoc 2017;6:e005435

Cumulative incidence of all-cause mortality and MACE



FH registries

Discovery of new monogenic/polygenic causes of FH phenotype

Study of treatment compliance and response

Correlation of genotype with phenotype

Understanding the natural history of FH

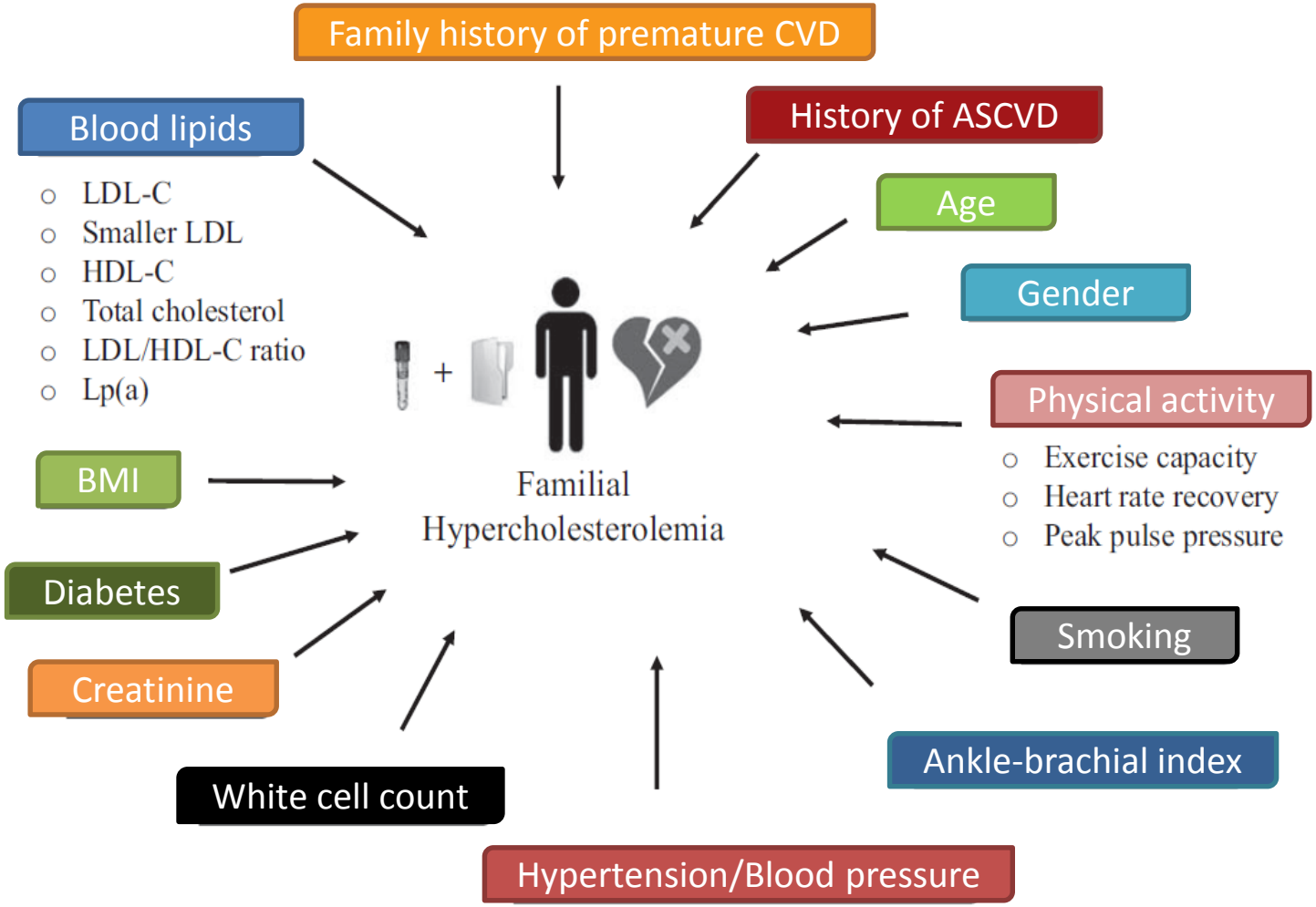
Local adaptation of diagnostic algorithms

Identification of factors modifying CV risk

FH registries

Attainment of LDL-Cholesterol Treatment Goals in Patients With Familial Hypercholesterolemia: 5-Year SAFEHEART Registry Follow-Up

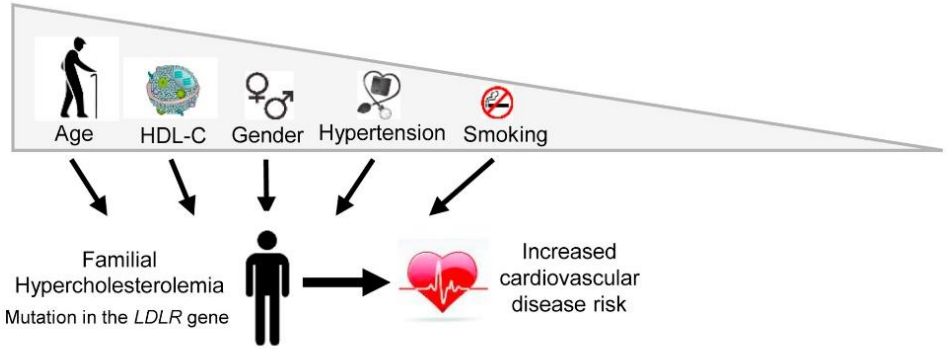
Perez de Isla, et al. J Am Coll Cardiol. 2016 Mar 22;67(11):1278-85



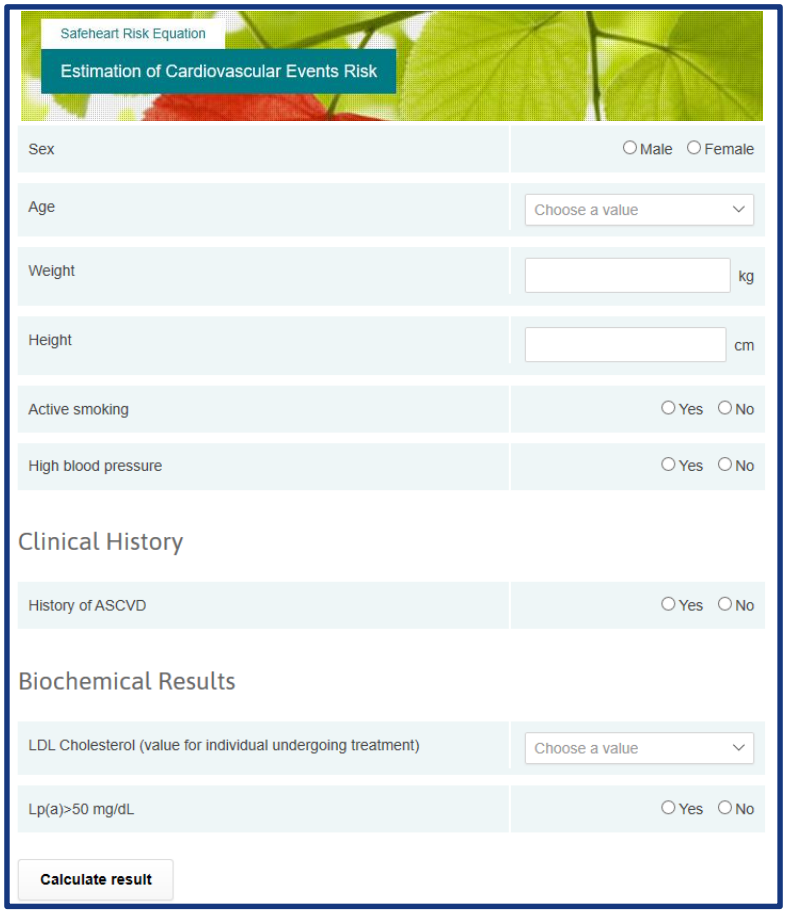
FH registries

The Montreal-FH-SCORE

Paquette M, et al. J Clin Lipidol. 2017



Combination of cardiovascular risk factors greatly increase CVD risk in familial hypercholesterolemia

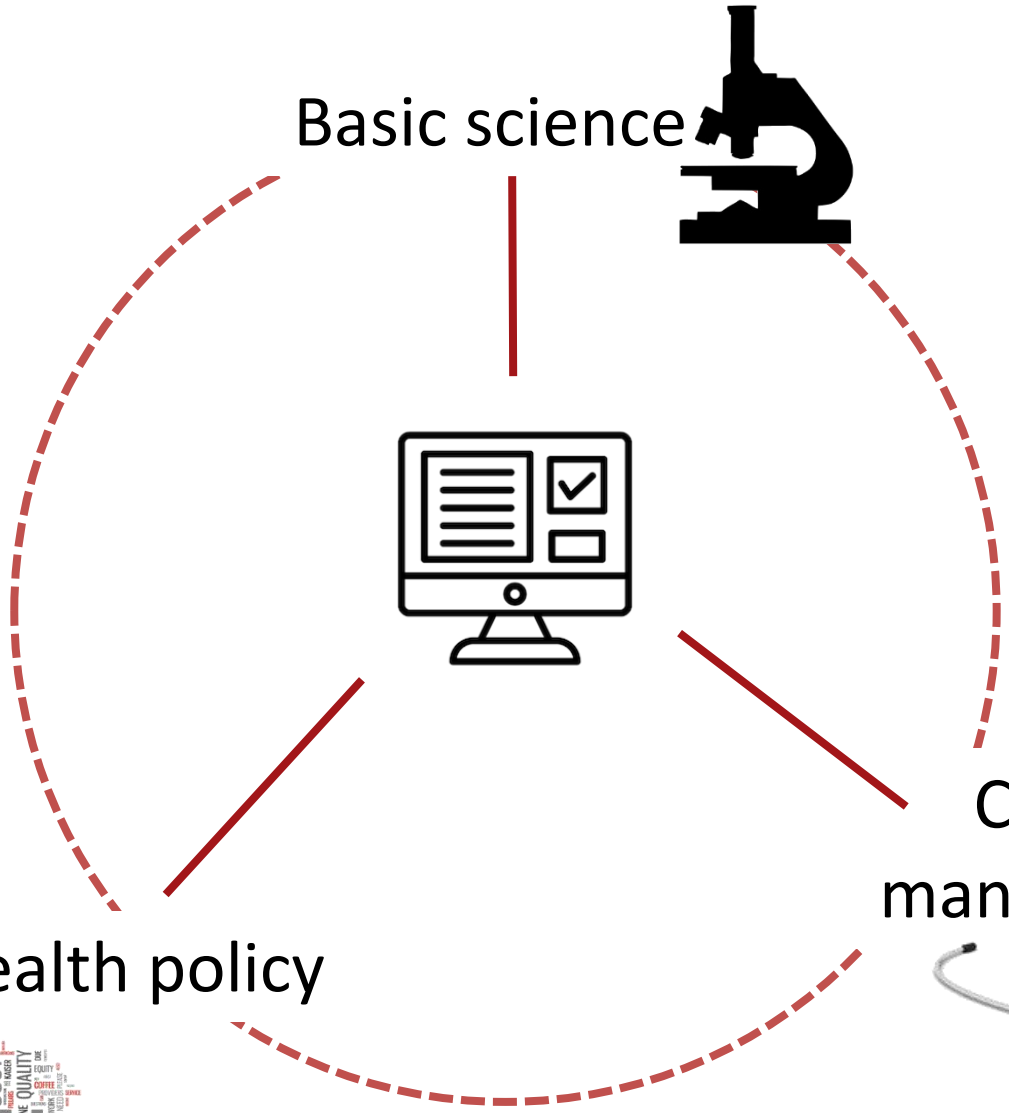


The SAFEHEART risk equation

Pérez de Isla L, et al. Circulation. 2017

FH registries

FH registries



Thanks

FONDAZIONE S.I.S.A.
per la promozione della ricerca sulle malattie da arteriosclerosi