

EAS



RUOLO DEI REGISTRI DI PATOLOGIA NELLA GESTIONE DELLE MALATTIE GENETICHE DEL METABOLISMO LIPIDICO E LIPID CLINIC NETWORK

Dott.ssa Manuela Casula
Università degli Studi di Milano



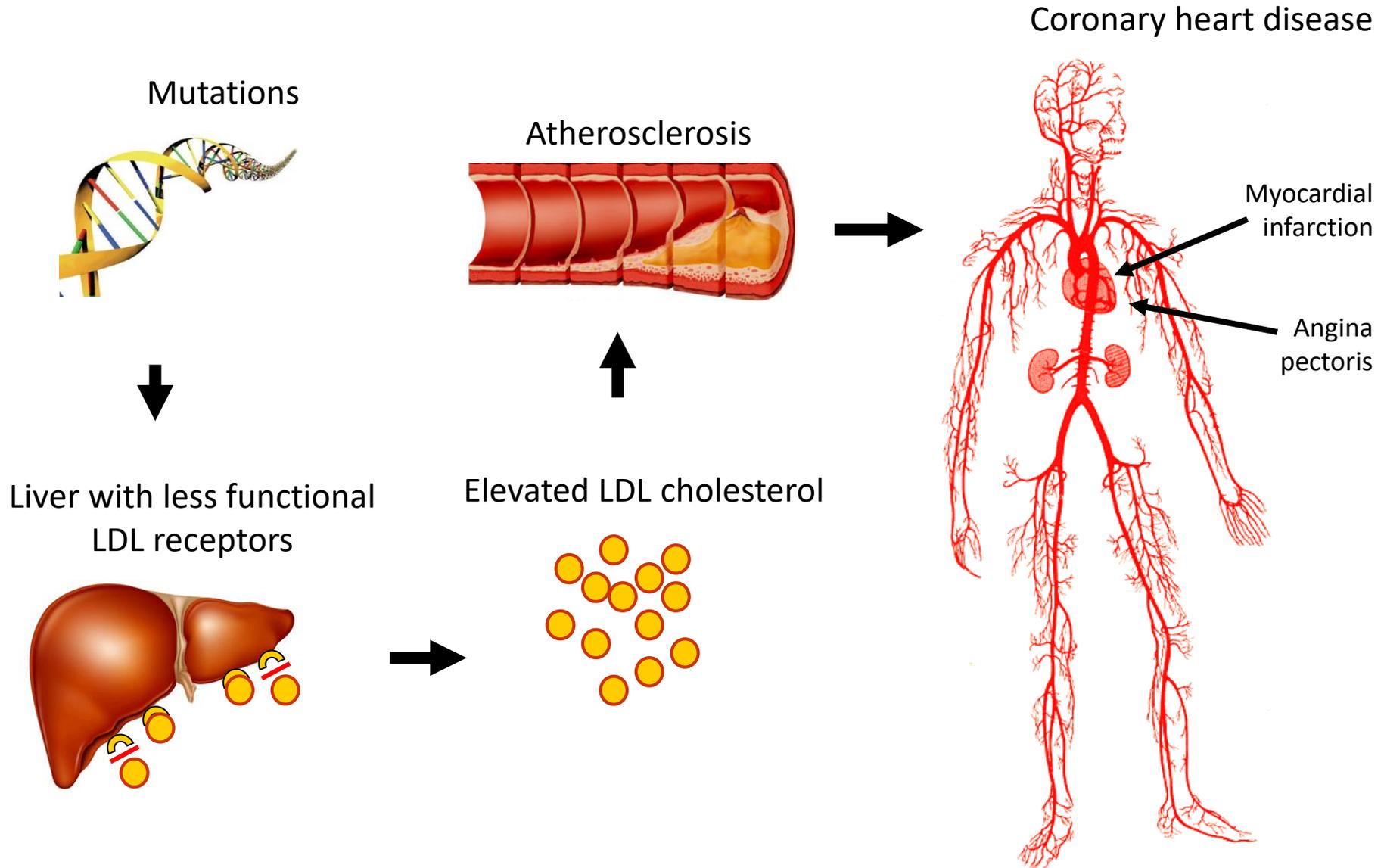
Ruolo dei registri di patologia nella gestione delle malattie genetiche del metabolismo lipidico e Lipid Clinic Network

Manuela Casula

DISCLOSURES

No relationships or conflicts to report.

Familial Hypercholesterolemia

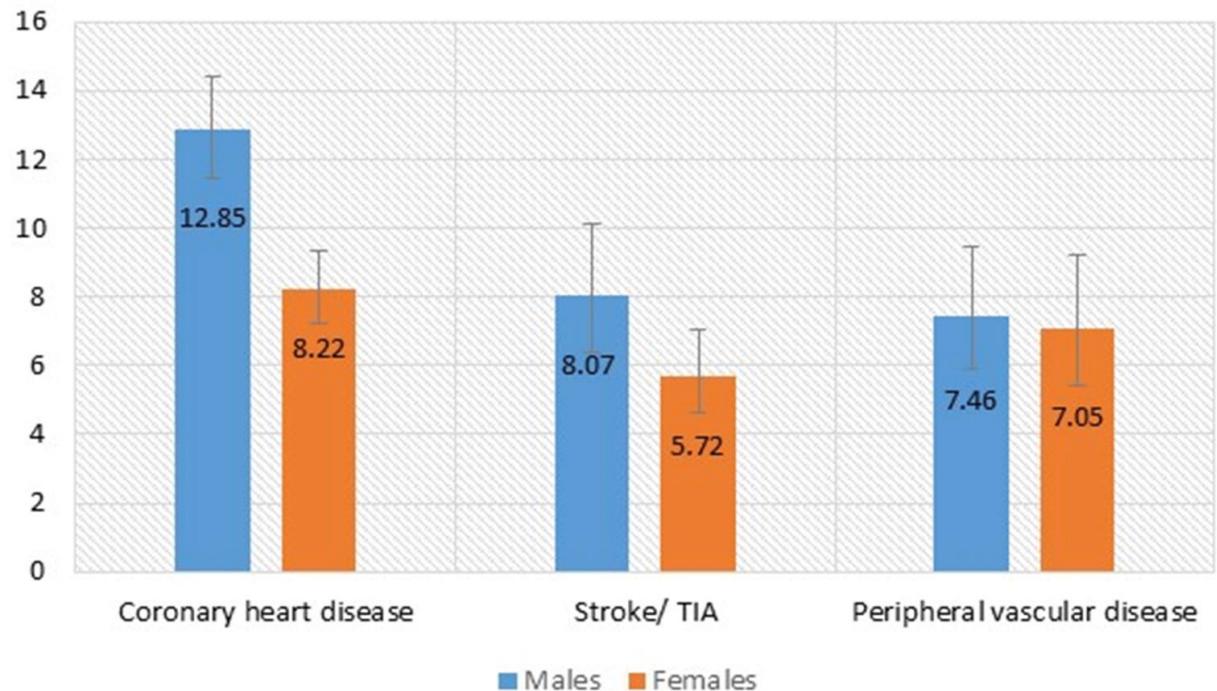


Familial hypercholesterolaemia: A global call to arms



Burden of disease

Hazards ratio for CVD outcomes in subjects with FH, stratified by sex

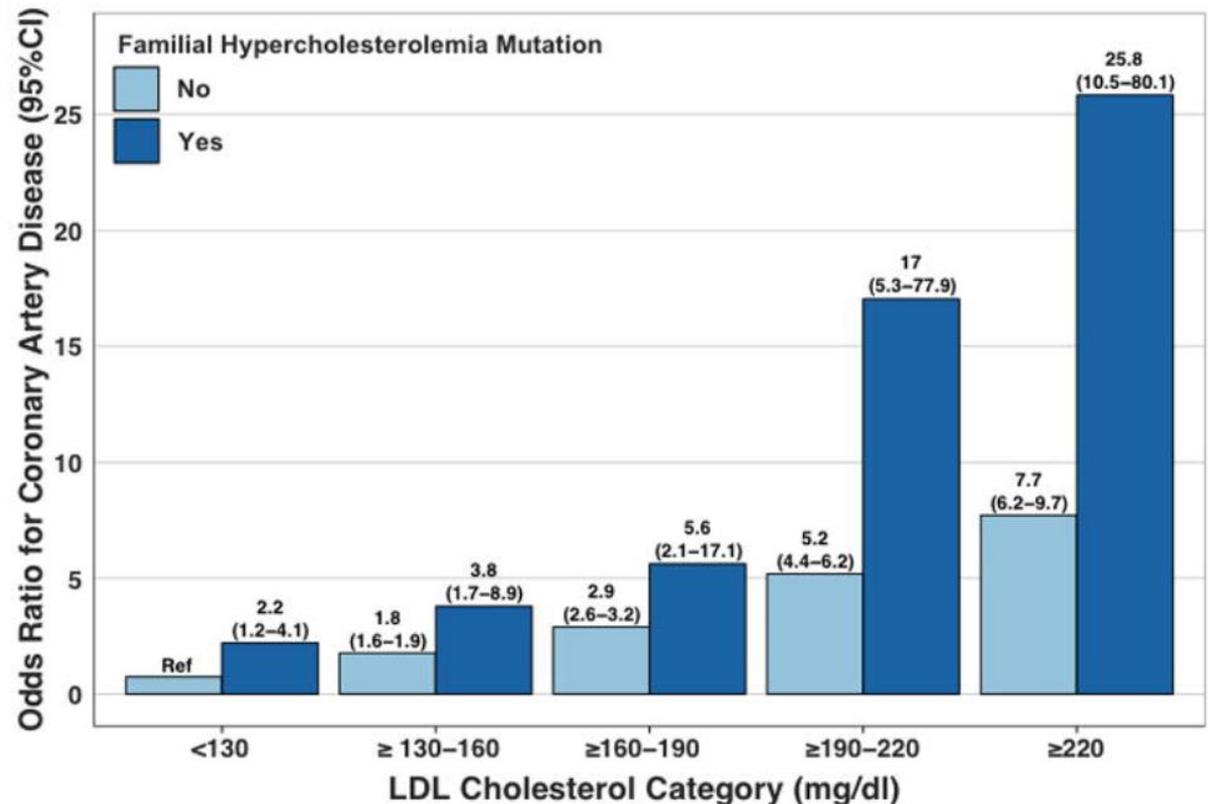


Familial hypercholesterolaemia: A global call to arms



Burden of disease

Impact of FH mutation status on CAD

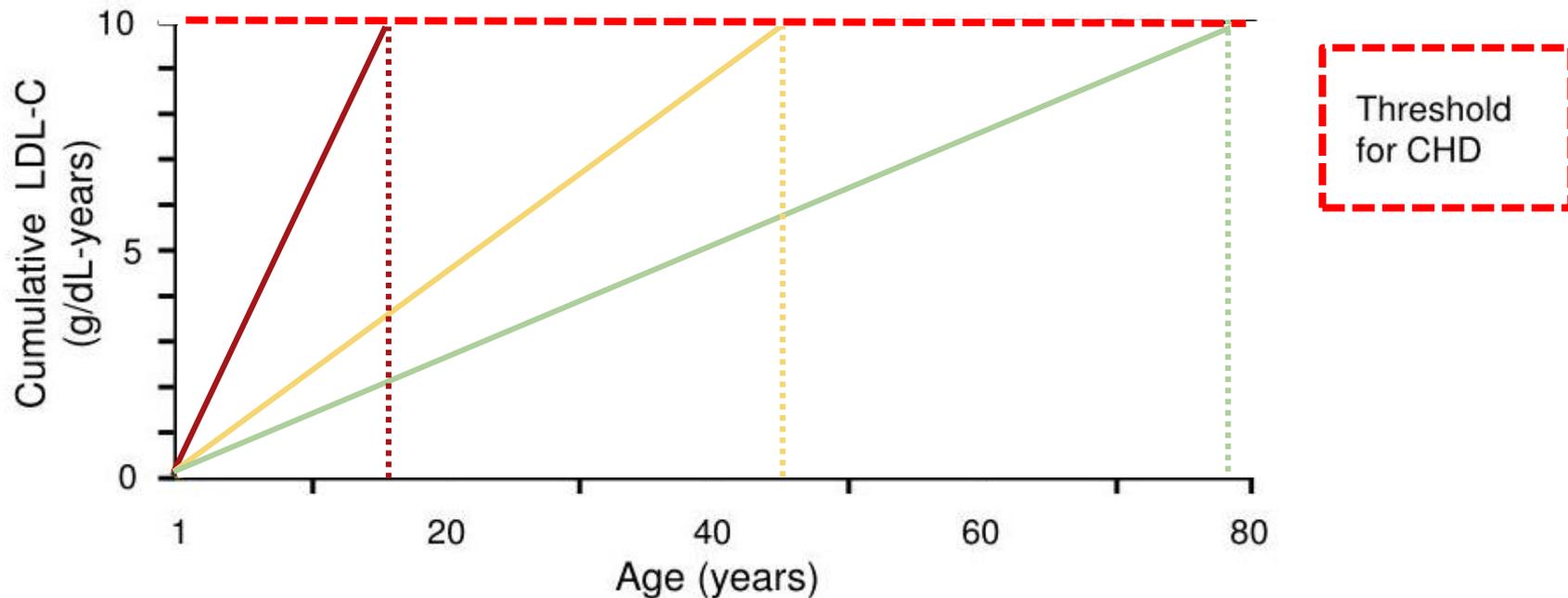


Familial hypercholesterolaemia: A global call to arms



Burden of disease

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

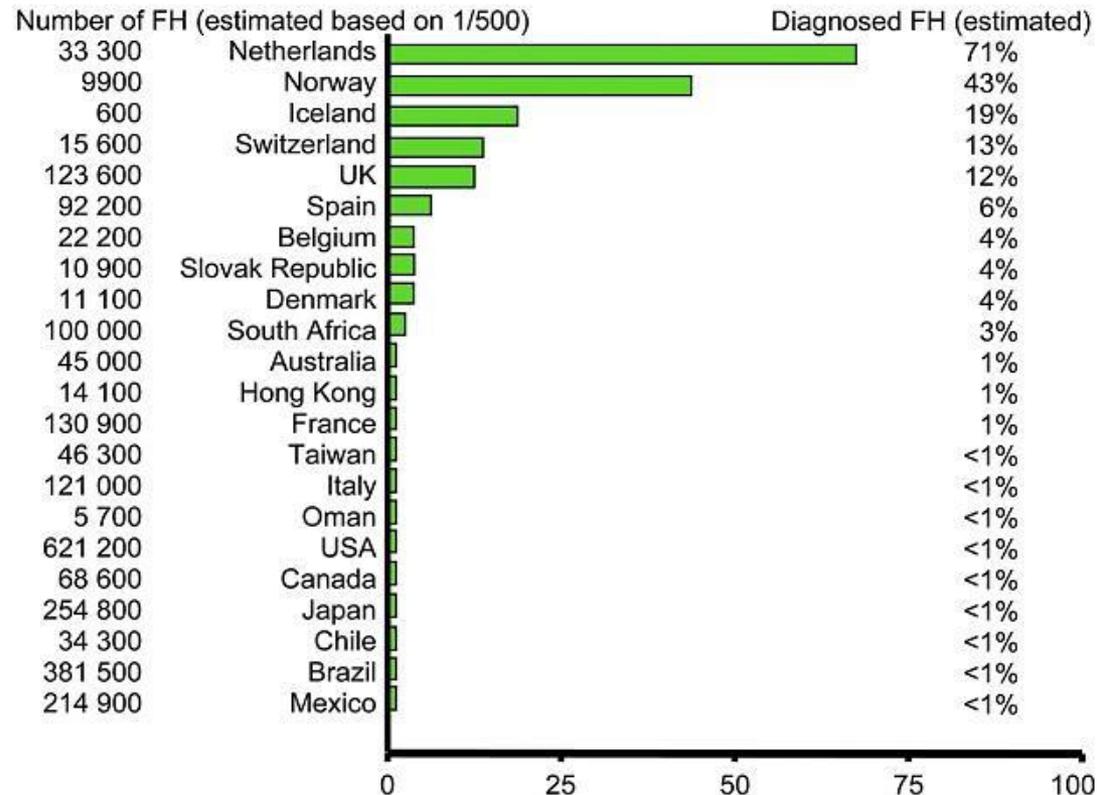


Familial hypercholesterolaemia: A global call to arms

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

Burden of disease

Estimated % of Individuals Diagnosed with FH



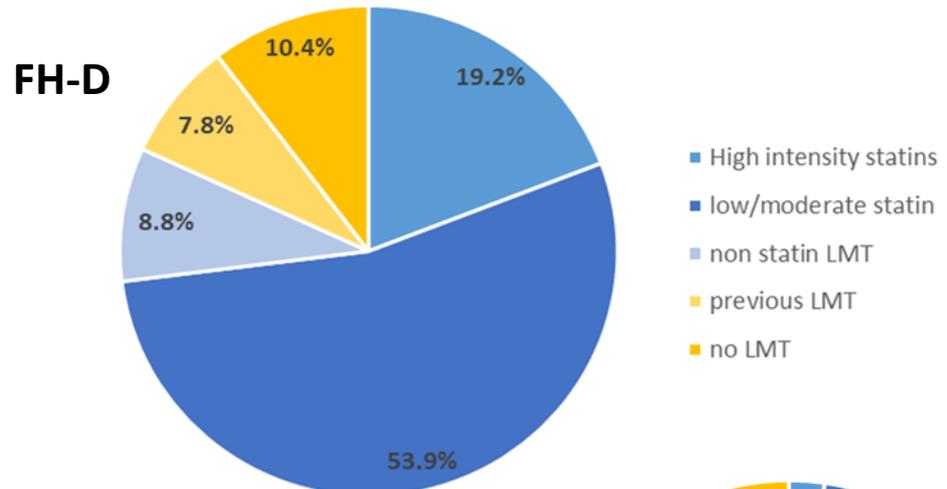
Underdiagnosed

Familial hypercholesterolaemia: A global call to arms

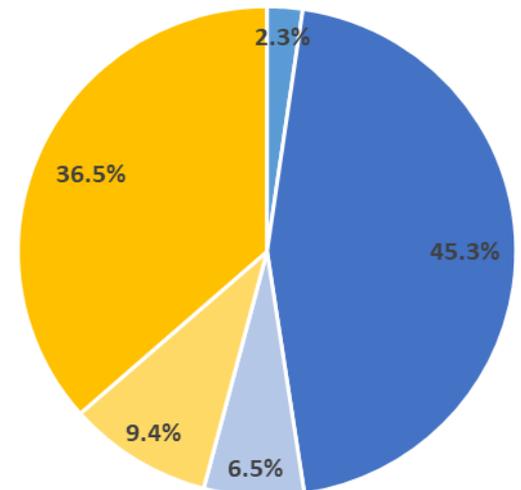
Cumulative incidence of all-cause mortality and major adverse cardiovascular events

Burden of disease

Underdiagnosed



FH-S



Undertreated

Familial hypercholesterolaemia: A global call to arms

Burden of disease

Underdiagnosed

Undertreated

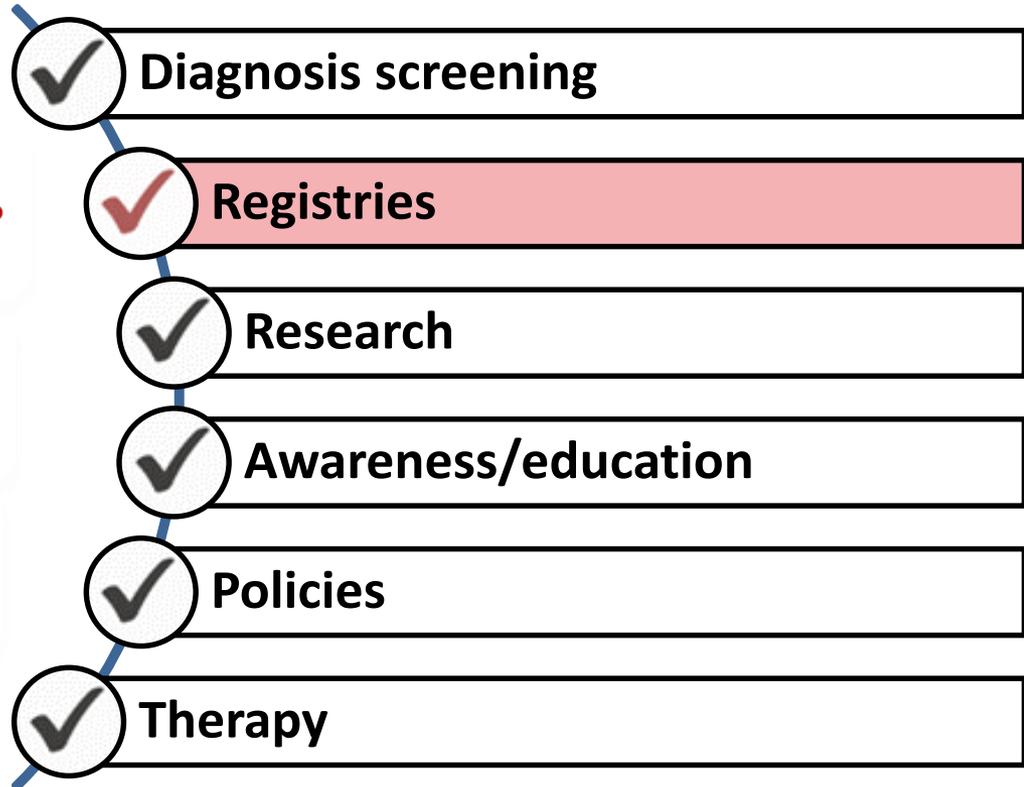
- ✓ Diagnosis screening
- ✓ Registries
- ✓ Research
- ✓ Awareness/education
- ✓ Policies
- ✓ Therapy

Familial hypercholesterolaemia: A global call to arms

Burden of disease

Underdiagnosed

Undertreated



FH registries

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



Open Access

AHJ
American Heart Journal

Spanish Familial
Cohort Study

vidio Muñiz⁵,
Mar Piedecausa⁹,
Mata^{2*}

HORMONES 2017, 16(3):306-312

al
Cascade Screening

Research paper

Atherosclerosis 277 (2018) 413–418

Contents lists available at ScienceDirect



ELSEVIER

journal homepage

An insight into
in Greece: rare
Hypercholesterolemia

Christos V. Rizos,¹ Vasiliki
Genovefa Kolovou,¹ Vasiliki
Ioannis Skoumas,^{1*}

Evaluation of the performance of
Italian FH population: The LIPIGEN

Manuela Casula^{a,b}, Elena Olmastroni^{a,b}, Angelo
of the LIPIGEN Group¹

^a Epidemiology and Preventive Pharmacology Centre (SEFAP), Department of
^b Department of Pharmacological and Biomolecular Sciences, University of Milan
^c Center for the Study of Atherosclerosis, E. Bassini Hospital, Cinisello Balsareto
^d IRCCS MultiMedica, Sesto S. Giovanni, Milan, Italy

frontiers
in Physiology

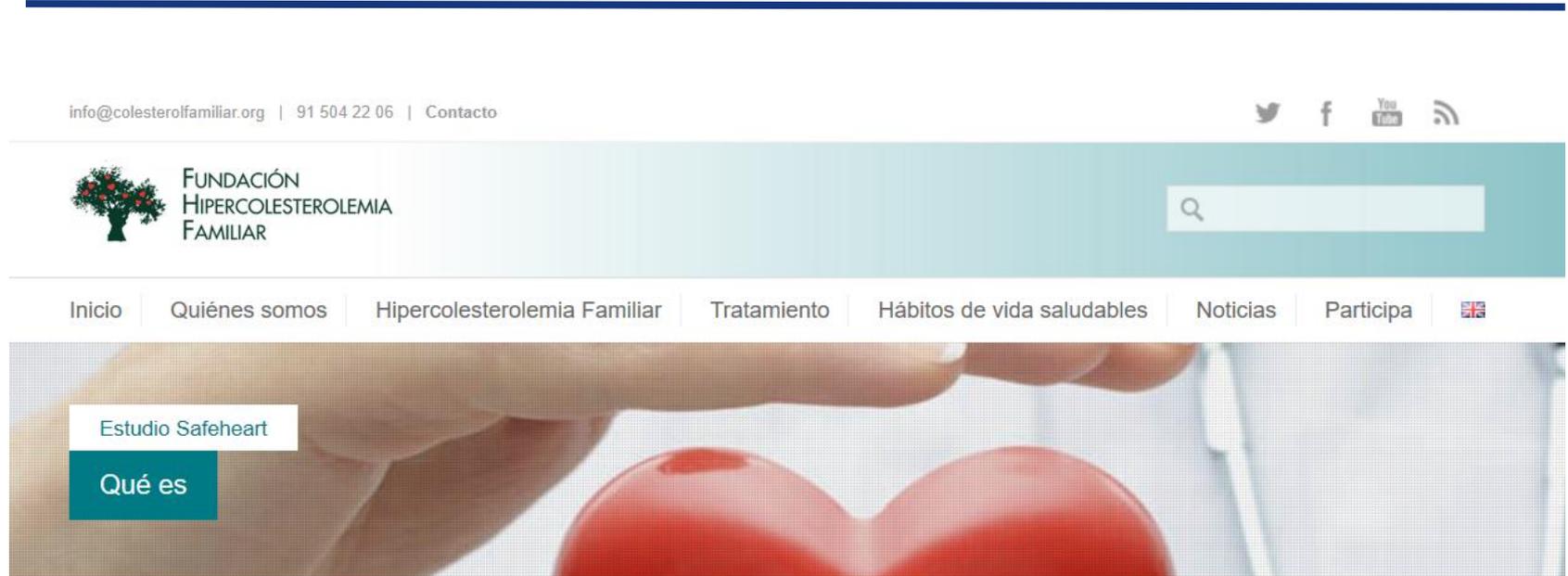
REVIEW
published: 20 March 2019
doi: 10.3389/fphys.2019.00280



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

Peipei Chen, Xi Chen and Shuyang Zhang*

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: 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: Canada FH registry



Get your free CardioRisk Calculator™ - FH Calculator app here



English (en) Français (fr)

Search

Home FH Canada Patients Health Care Professionals About Us Get Involved Contact Us CCS Position Statement on FH
New Canadian Definition of FH Report of Activities

FH Canada **Registry**



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

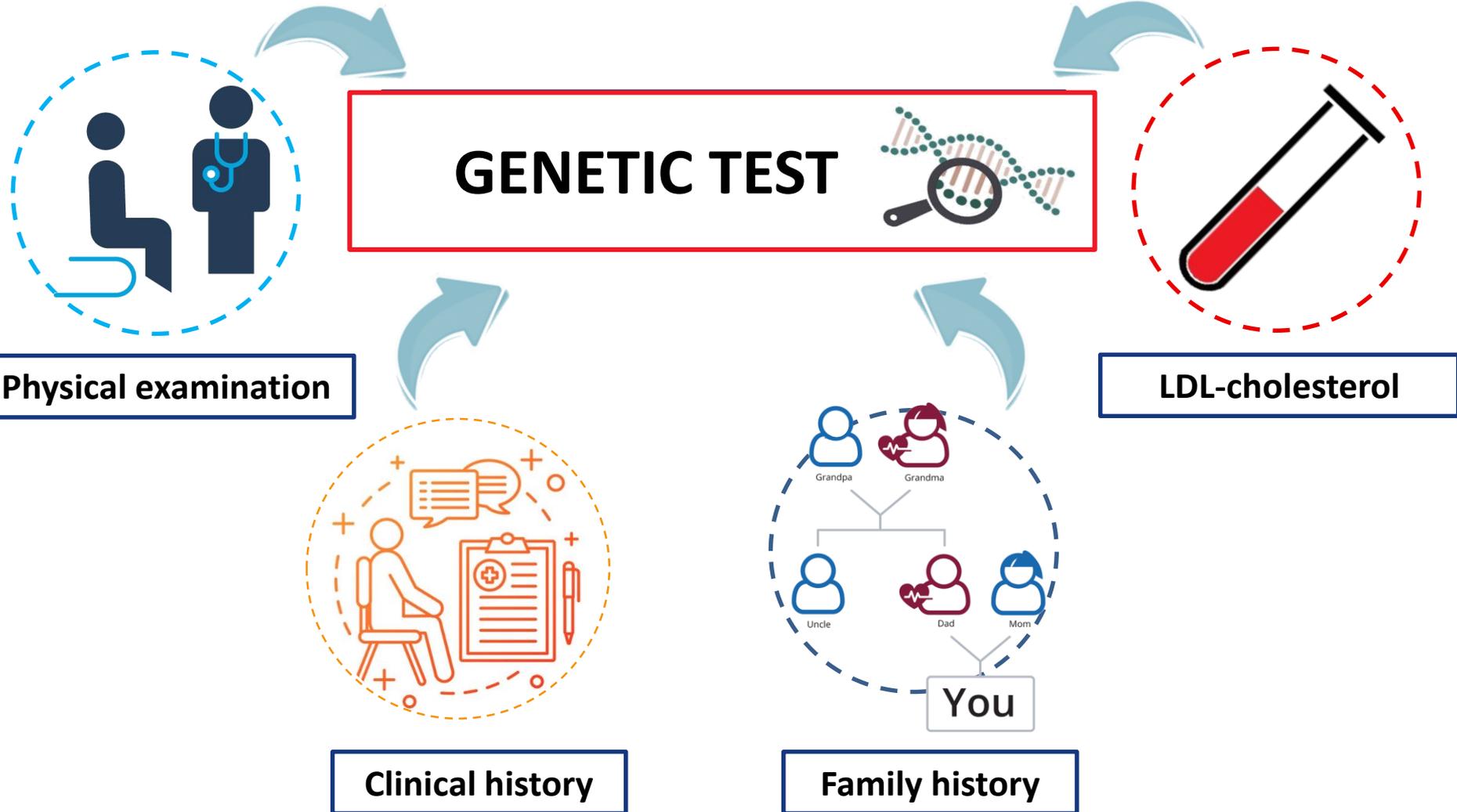
FH registries: LIPIGEN study



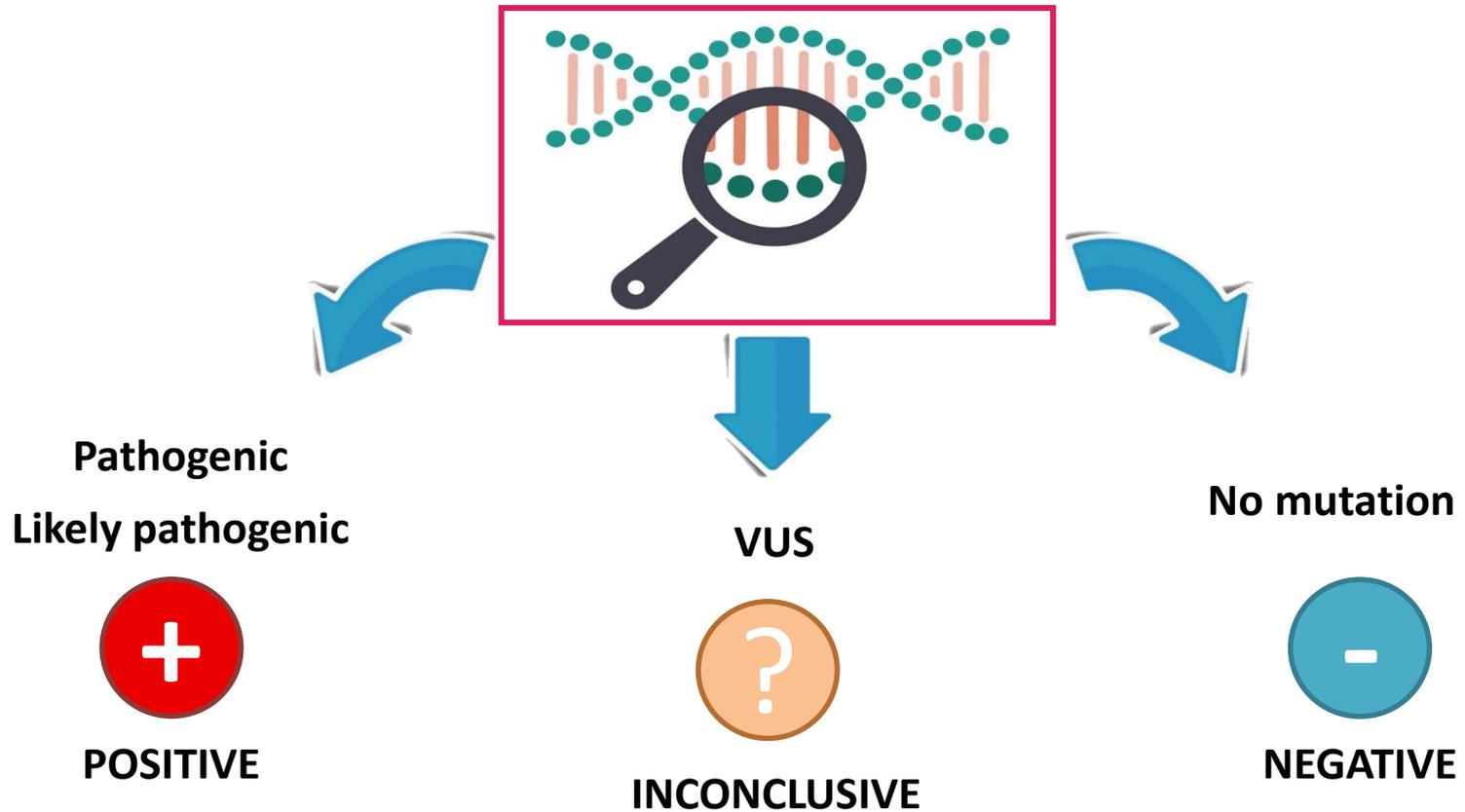
The **Lipid TransPort Disorders Italian GENetic Network (LIPIGEN) - Registro delle Dislipidemie Familiari in Italia** is an observational, multicentric, retrospective and prospective study, aimed at creating an Italian Database of Familial Hypercholesterolemia.

FH patients are included if they receive clinical **and/or** genetic diagnosis

FH registries: LIPIGEN study



FH registries: LIPIGEN study

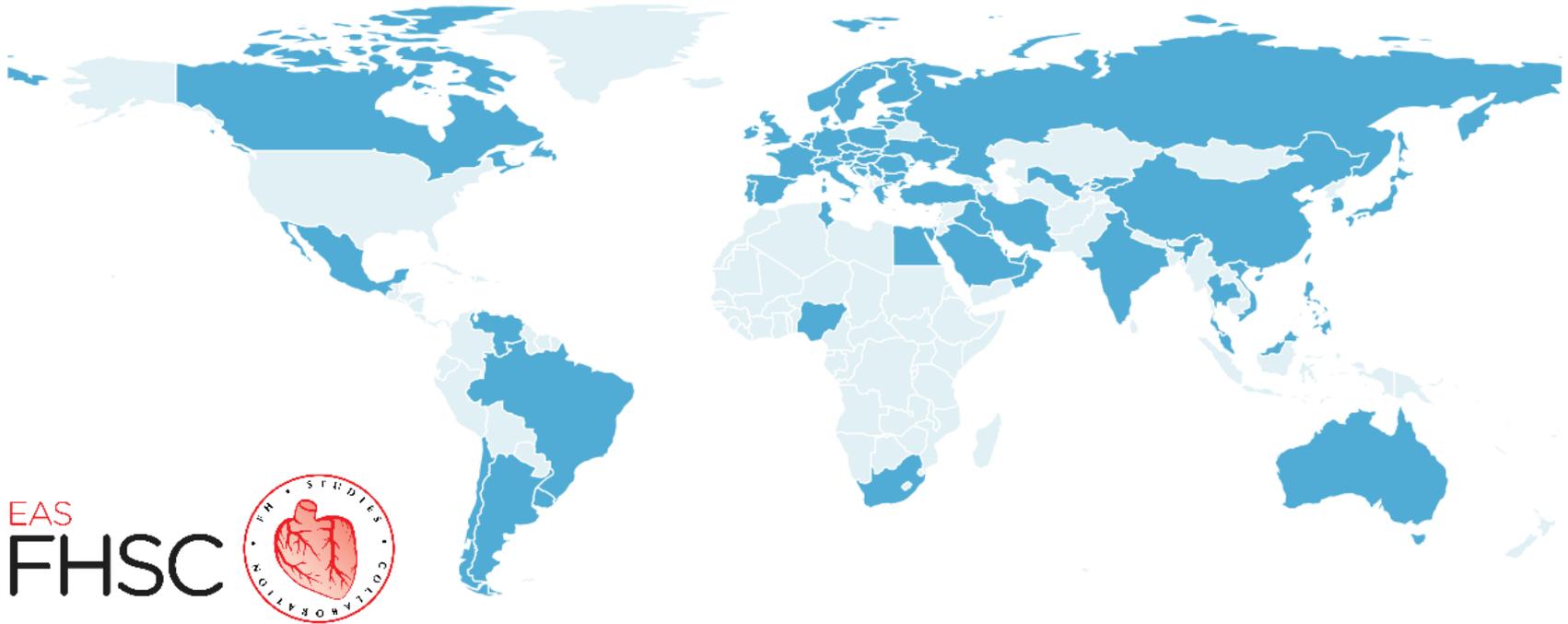




Pooling and expanding registries of familial hypercholesterolaemia to assess gaps in care and improve disease management and outcomes: Rationale and design of the global EAS Familial Hypercholesterolaemia Studies Collaboration

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 Soranⁱ, Tomas Freiburger^{j,k}, Marianne Abifadel^l, Carlos A. Aguilar-Salinas^m, Fahad Alnouriⁿ, 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 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

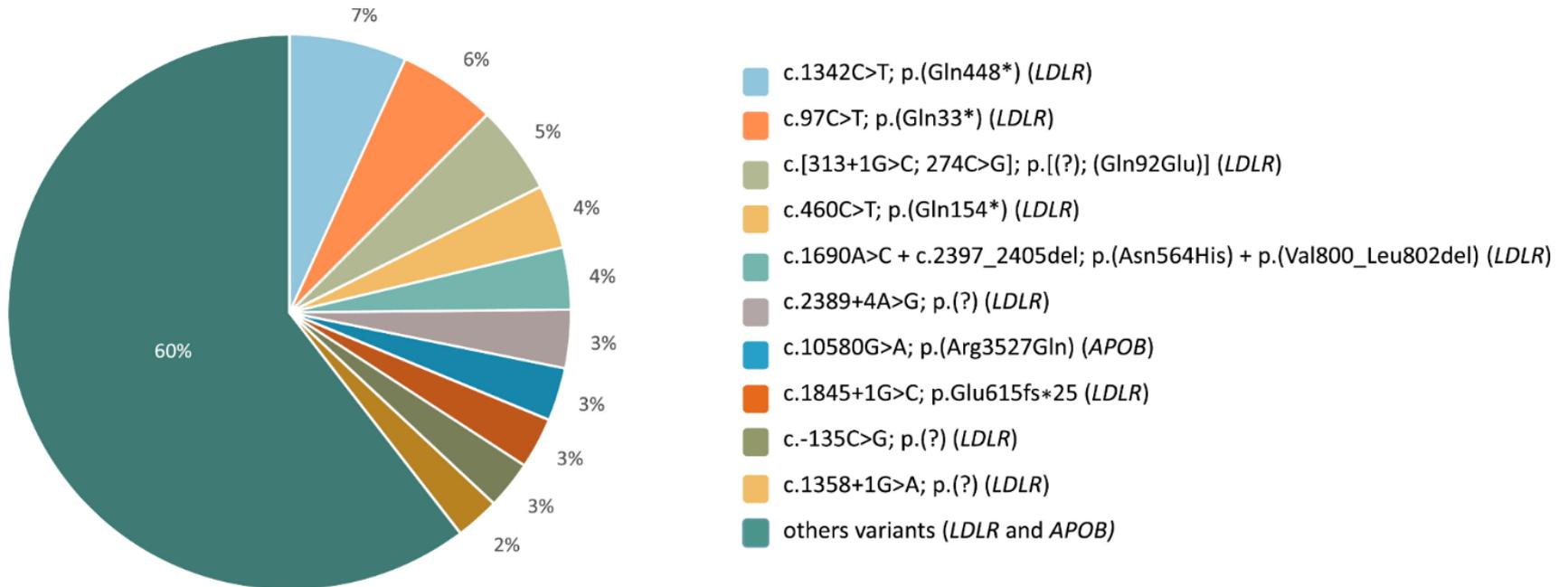


FH registries

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 <i>in silico</i> classification of the 24 new alterations found in this study.						
cDNA	Protein	Gene	Alteration type	Overall <i>in silico</i>	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.(Met11le)
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)

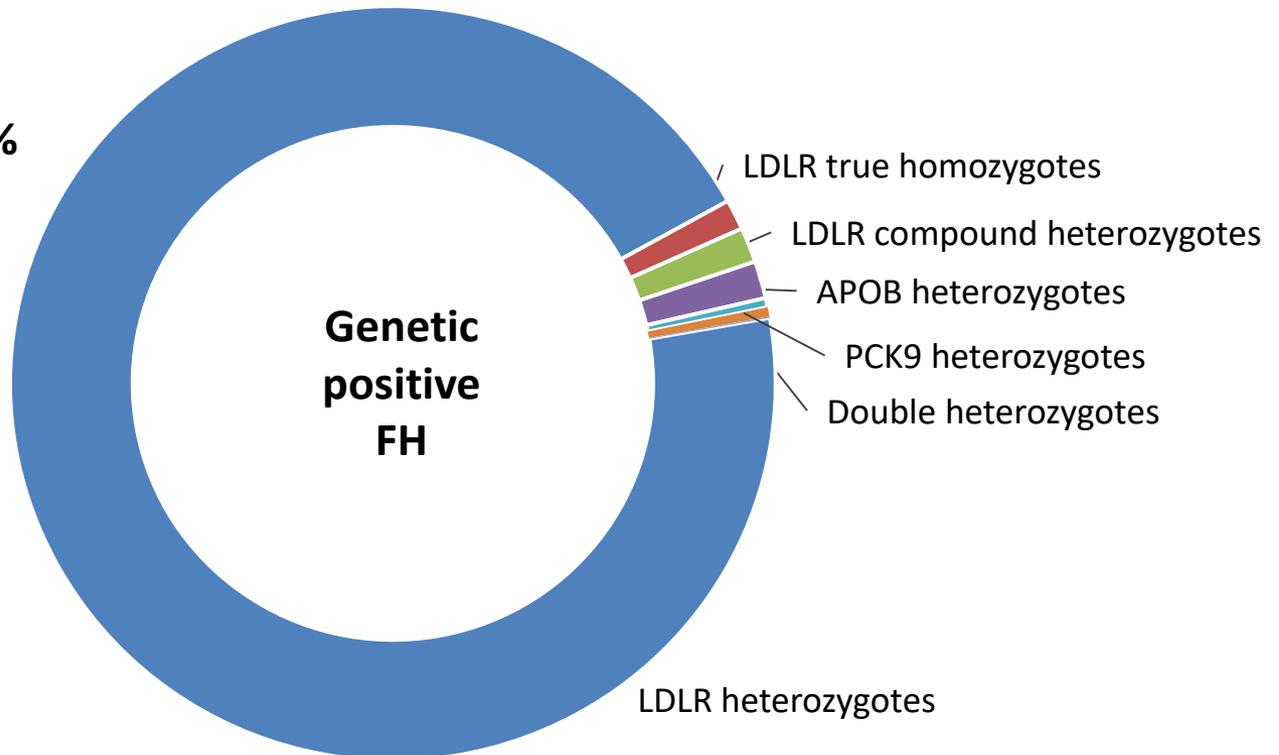
In silico analysis of missense mutations was performed using PolyPhen-2 HumDiv and Hum Var (<http://genetics.bwh.harvard.edu/pph2/>), SIFT Human Protein (<http://sift.jcvi.org/>) and Mutation Taster (www.mutationtaster.org/). The potential effect of an intronic variant on pre-mRNA splicing was assessed by Human Splicing Finder (<http://www.umd.be/HSF3/HSF.html>), NetGene2 (<http://www.cbs.dtu.dk/services/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

LIPIGEN

Almost the whole cohort (98%) underwent genetic testing.

Negative: 18%
Inconclusive: 12%
Positive: 70%



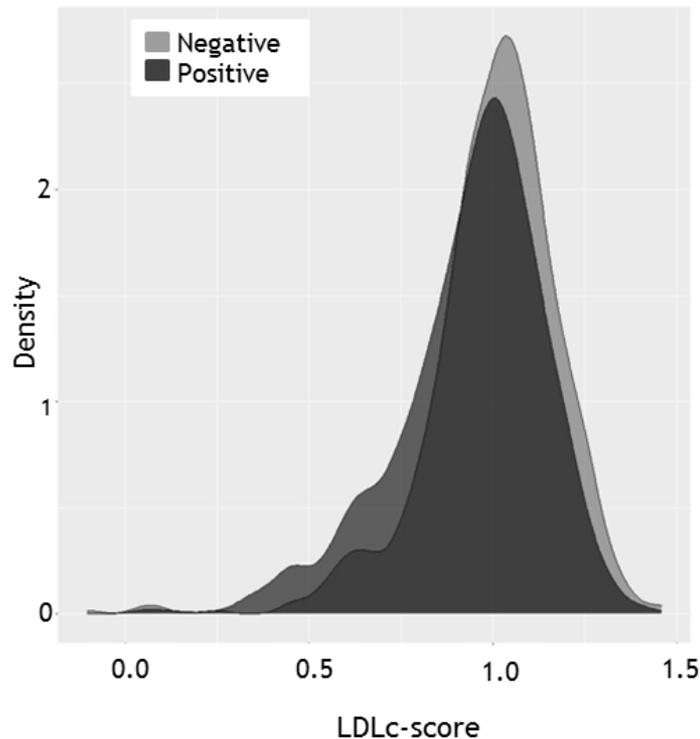
FH registries

A 12 variants polygenic score for ldl cholesterol distribution in a large cohort of patients with clinically diagnosed familial hypercholesterolemia with or without causative mutations

Olmastroni A, et al. *manuscript submitted*

LDL-C score (12 SNPs) for polygenic hypercholesterolemia

The mean value of LDLc-score was significantly higher in FH/M- compared to FH/M+



FH/M-, N=644
mean (SD)
1.00 (0.18)

FH/M+, N=875
mean (SD)
0.94 (0.20)

p-value<0.001

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

Homozygous familial hypercholesterolemia in Italy: Clinical and molecular features.

Bertolini S, et al. Atherosclerosis. 2020 Nov;312:72-78

A total of 125 subjects with ADH were identified, of whom 60 were true homozygotes, 58 compound heterozygotes and 7 double heterozygotes for LDLR (likely) pathogenic variants.



Untreated LDL-C levels [md/dL], mean \pm SD

	D-HeFH	C-HeFH	HoFH
Defective	251.93 \pm 84.13	421.48 \pm 156.42	499.65 \pm 180.98
Null	308.73 \pm 42.52	573.17 \pm 277.24	800.27 \pm 253.26
TOTAL	273.23 \pm 73.66	471.17 \pm 213.87	576.08 \pm 239.15

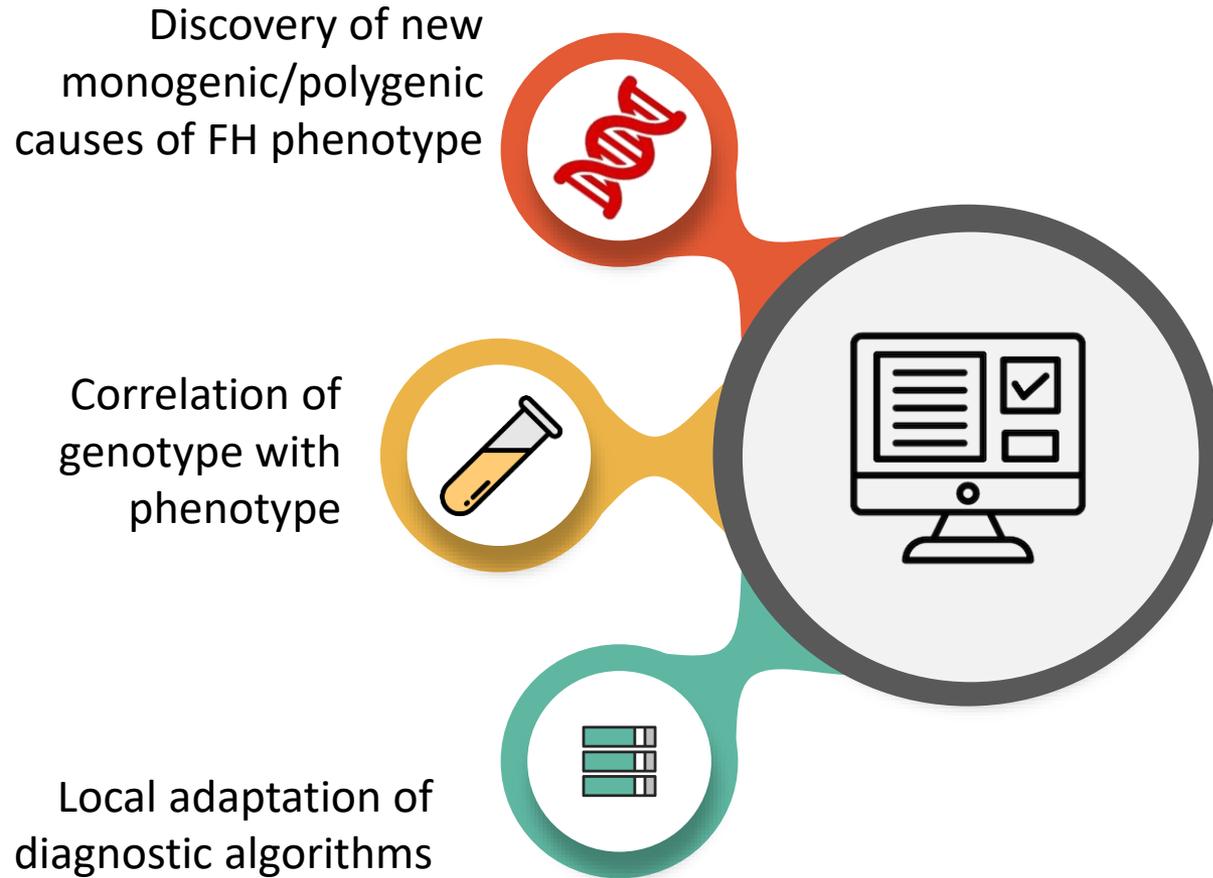
Personal history of CVD, %

		D-HeFH	C-HeFH	HoFH
Cardiovascular disease	Defective	20.0%	44.7%	55.8%
	Null	33.3%	52.9%	80.0%
	TOTAL	25.0%	47.3%	62.1%
Cerebro-vascular or peripheral disease	Defective	0%	12.9%	23.5%
	Null	0%	10.0%	33.3%
	TOTAL	0%	12.2%	25.0%

Physical signs of FH, %

		D-HeFH	C-HeFH	HoFH
Xanthomas	Defective	0%	64.9%	74.4%
	Null	33.3%	76.5%	100.0%
	TOTAL	12.5%	68.5%	80.7%
Arcus cornealis	Defective	0%	35.5%	23.5%
	Null	33.3%	55.6%	33.3%
	TOTAL	12.5%	40.0%	25.0%

FH registries



FH registries

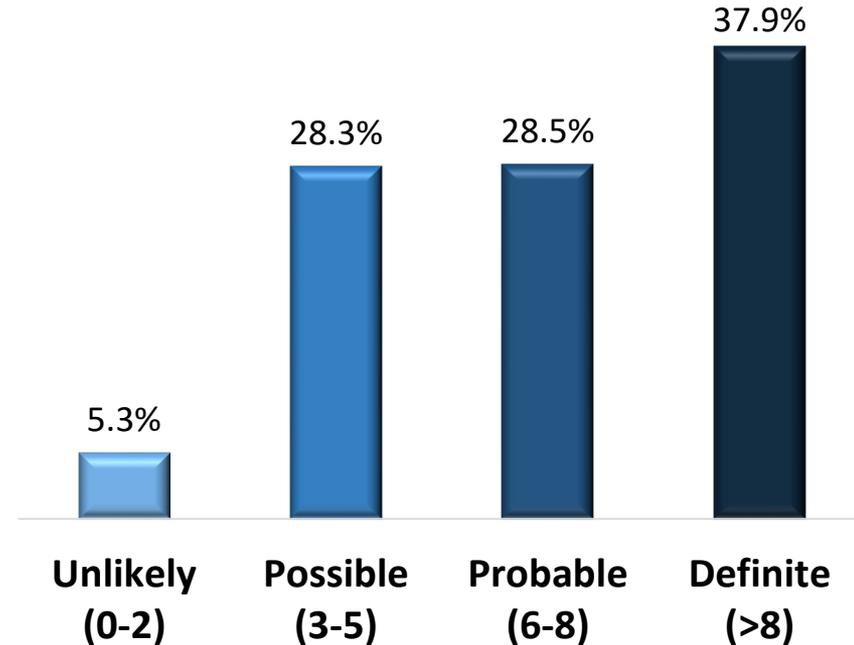
Evaluation of the performance of Dutch Lipid Clinic Network score in an Italian FH population: The LIPIGEN study.

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

Criteria	Missing(%)
First-degree relative with known premature CHD	11.62
First-degree relative with known LDL cholesterol >95° percentile	12.85
First-degree relative with tendon xanthoma and/arcus cornealis	34.57
Child(ren) <18 years with LDL cholesterol >95° percentile	25.78
Subject has premature CHD	9.08
Subject has premature cerebral or peripheral vascular disease	10.17



FH registries

Heterozygous familial hypercholesterolemia. Relationship between plasma lipids, lipoproteins, clinical manifestations and ischaemic heart disease in men and women.

Gagné C, et al. Atherosclerosis. 1979 Sep;34(1):13-24

A large cohort of 264 men and 311 women with heterozygous FH (mostly French Canadians) was seen between 1972 and 1978

Age groups sex	N ^a	Tendinous xanthomas	Ischaemic heart disease
<20	M	2 (2)	0
	F	2 (4)	0
20–29	M	22 (49)	8 (18) **
	F	15 (36)	0
30–39	M	32 (63)	18 (35) **
	F	41 (75)	6 (11)
40–49	M	39 (89)	28 (64) **
	F	41 (91)	15 (33)
>50	M	26 (81)	18 (56)
	F	44 (77)	31 (54)
>20	M	119 (69)	72 (42) **
	F	141 (71)	52 (26)



LIPIGEN

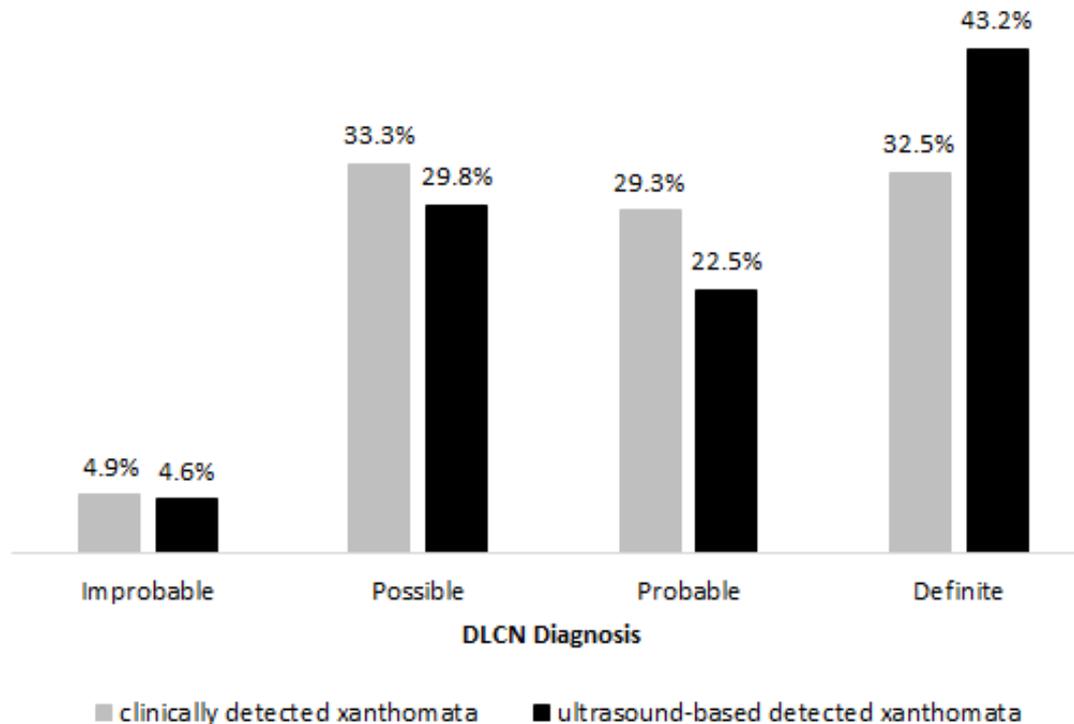
- 13% among over18

FH registries

The Achilles tendon ultrasonography in familial hypercholesterolemia: results from a sub-study of the Lipid transport disorders Italian Genetic Network (LIPIGEN)

Baragetti A, et al. *manuscript submitted*

Reclassification of DLCN categories by ultrasound-based analysis of Achilles tendon xanthomas



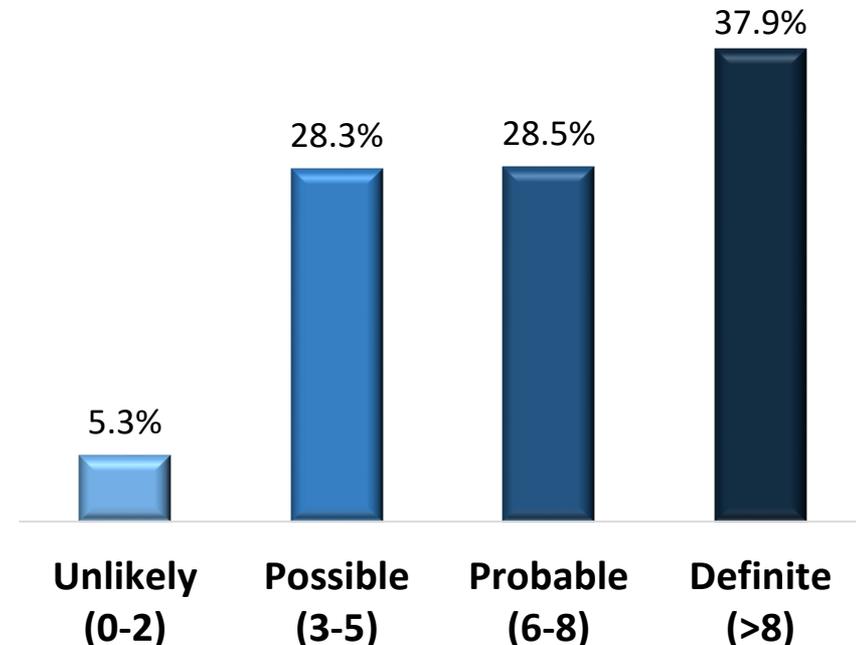
FH registries

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

	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

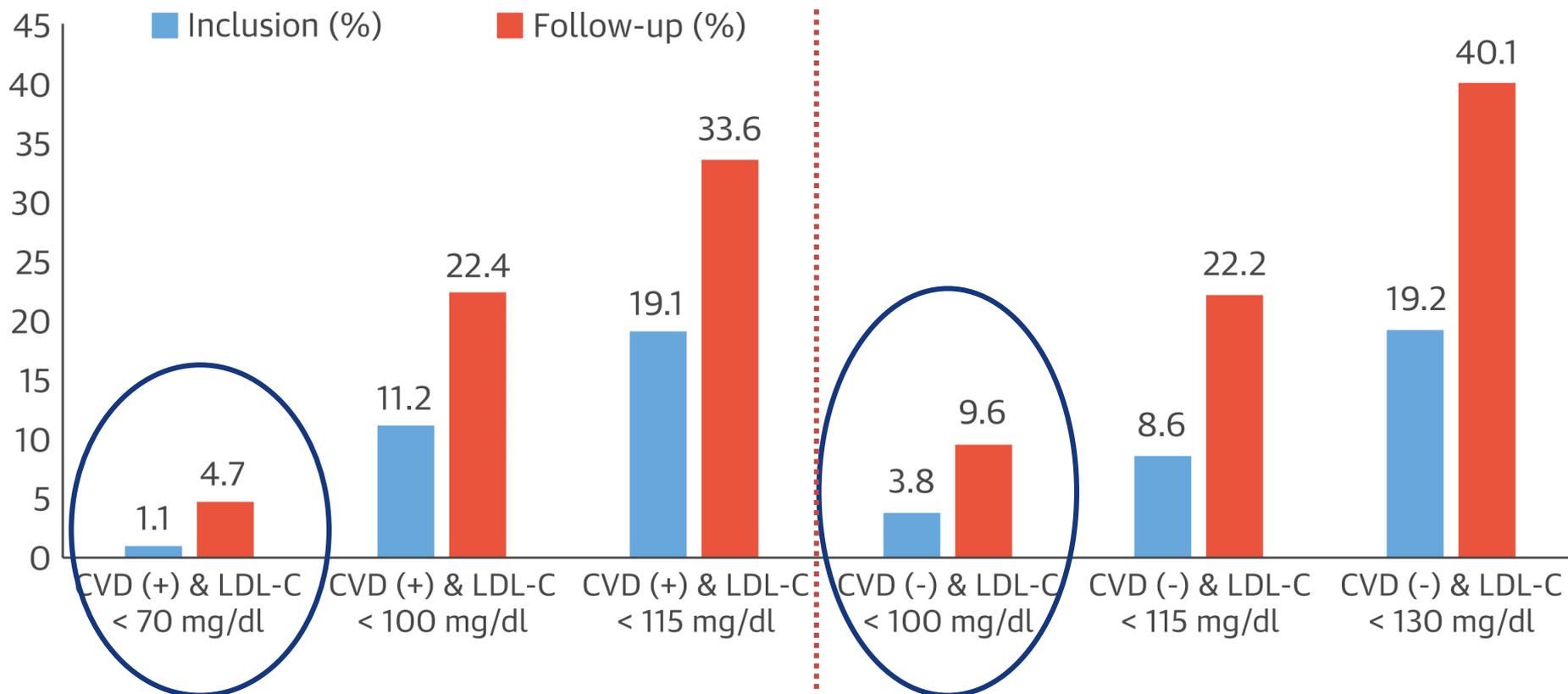


FH registries

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

Percentage of Patients Reaching Recommended Goals



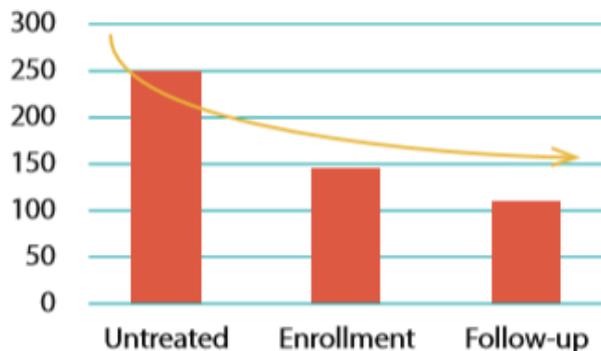
FH registries

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 $\frac{2}{3}$ 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

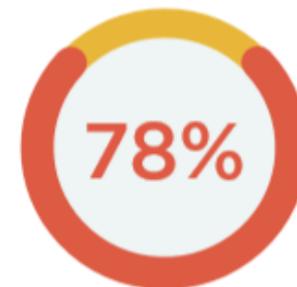
Mean LDL-C Results Over Time



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

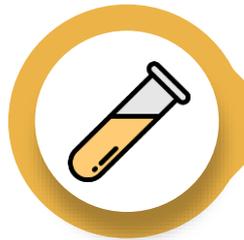
Discovery of new monogenic/polygenic causes of FH phenotype



Study of treatment compliance and response



Correlation of genotype with phenotype



Analysis of specific subgroups



Local adaptation of diagnostic algorithms



FH registries

Children with Heterozygous Familial Hypercholesterolemia in the United States: Data from the Cascade Screening for Awareness and Detection-FH Registry

de Ferranti SD, et al. J Pediatr. 2021 Feb;229:70-77



Diagnosis comes late

Diagnosis at 9 years, despite recommendations to begin screening at age 2

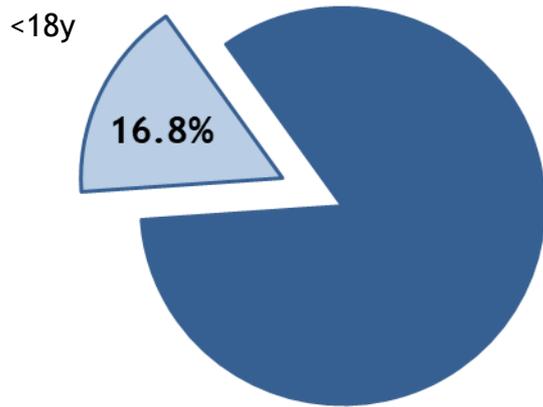


Treatment goals missed

Only 39% of the youth achieved recommended LDL-C reduction

FH registries

LIPIGEN paediatric group



31 lipid
clinics

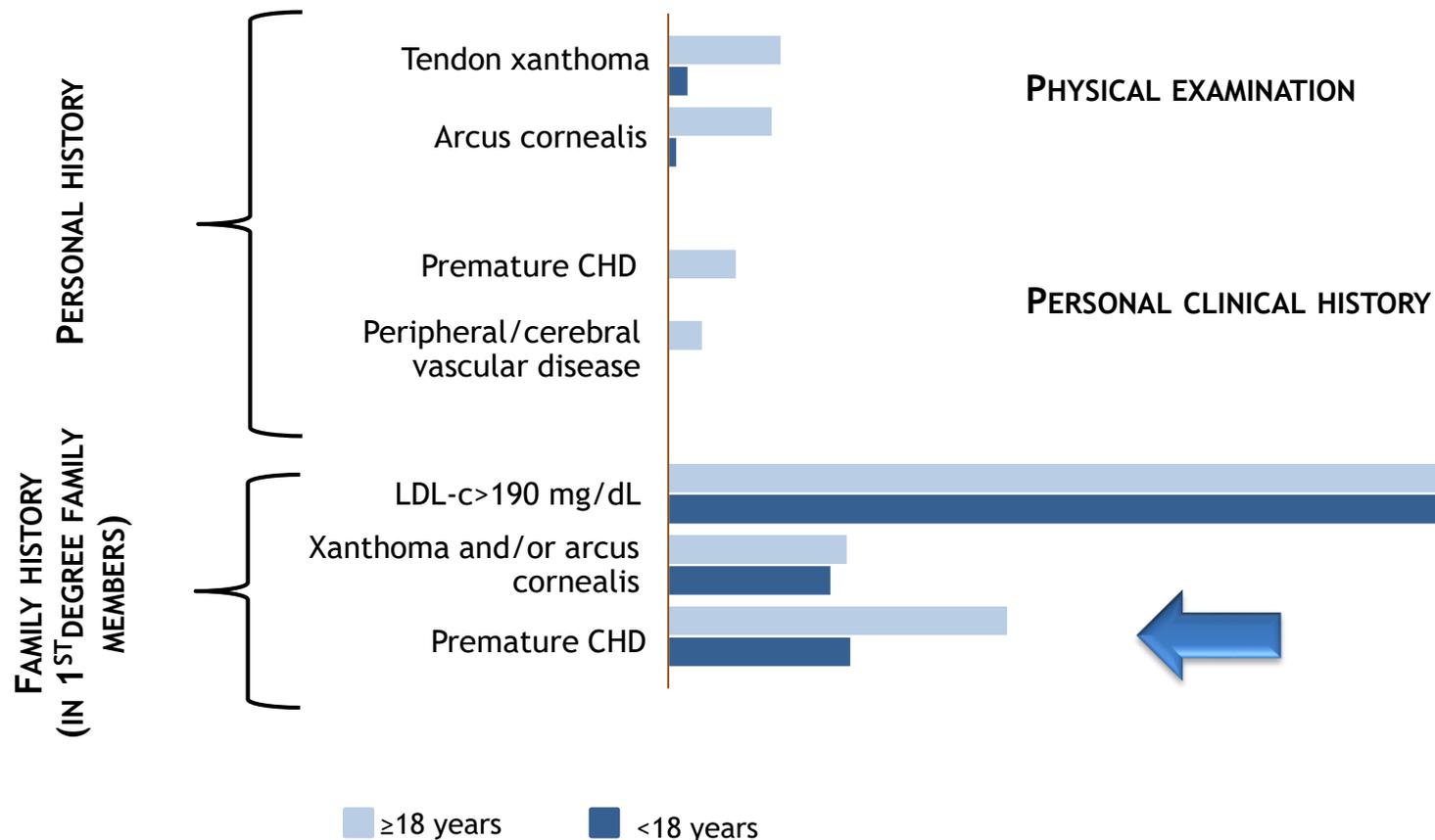


- ✓ To identify and propose specific changes in the collection, analysis and interpretation of the data in eCRF
- ✓ To promote improvements in the screening, diagnosis and treatment of pediatric FH subjects
- ✓ To propose recommendations to support clinical practice

FH registries

LIPIGEN

Lower prevalence of typical FH features in children/adolescents vs adults and the absence of personal history of premature CHD or cerebral/peripheral vascular disease



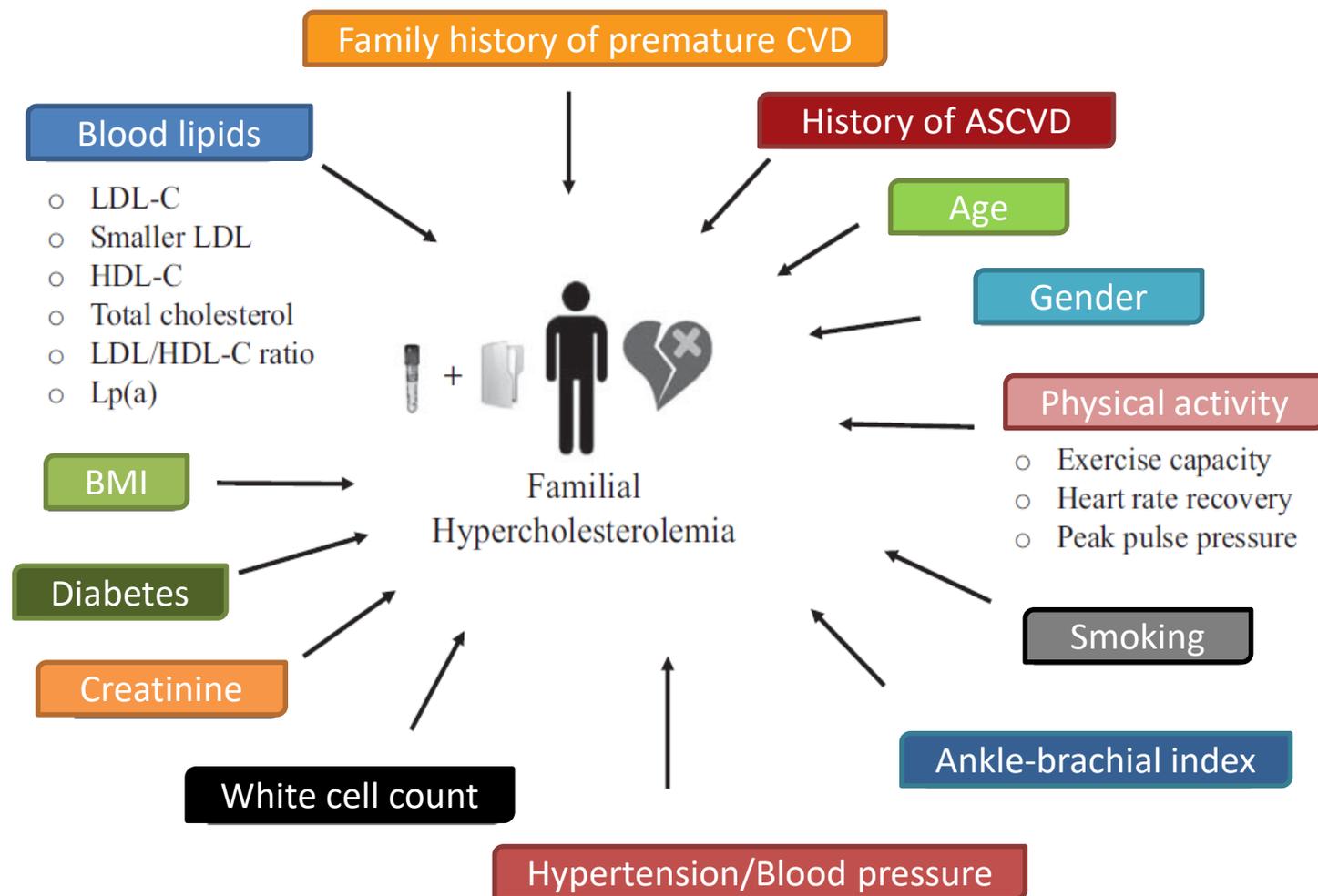
FH registries



FH registries

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

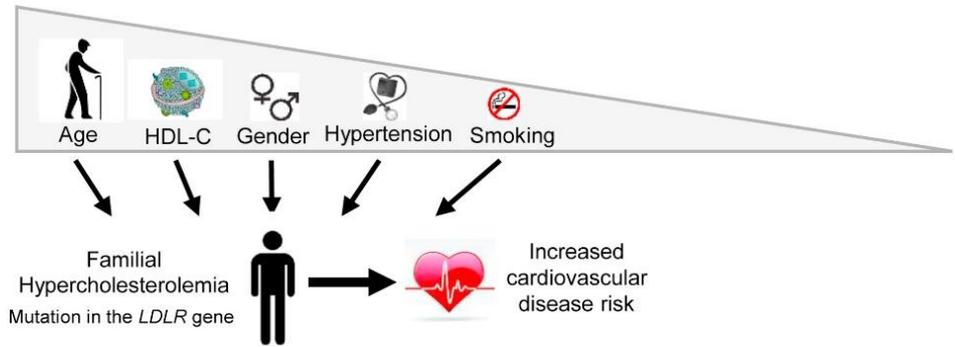
Perez de Isla, et al. J Am Coll Cardiol. 2016 Mar 22;67(11):1278-85



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

Safeheart Risk Equation

Estimation of Cardiovascular Events Risk

Sex	<input type="radio"/> Male <input type="radio"/> Female
Age	Choose a value <input type="text"/>
Weight	<input type="text"/> kg
Height	<input type="text"/> cm
Active smoking	<input type="radio"/> Yes <input type="radio"/> No
High blood pressure	<input type="radio"/> Yes <input type="radio"/> No

Clinical History

History of ASCVD	<input type="radio"/> Yes <input type="radio"/> No
------------------	--

Biochemical Results

LDL Cholesterol (value for individual undergoing treatment)	Choose a value <input type="text"/>
Lp(a)>50 mg/dL	<input type="radio"/> Yes <input type="radio"/> No

Calculate result

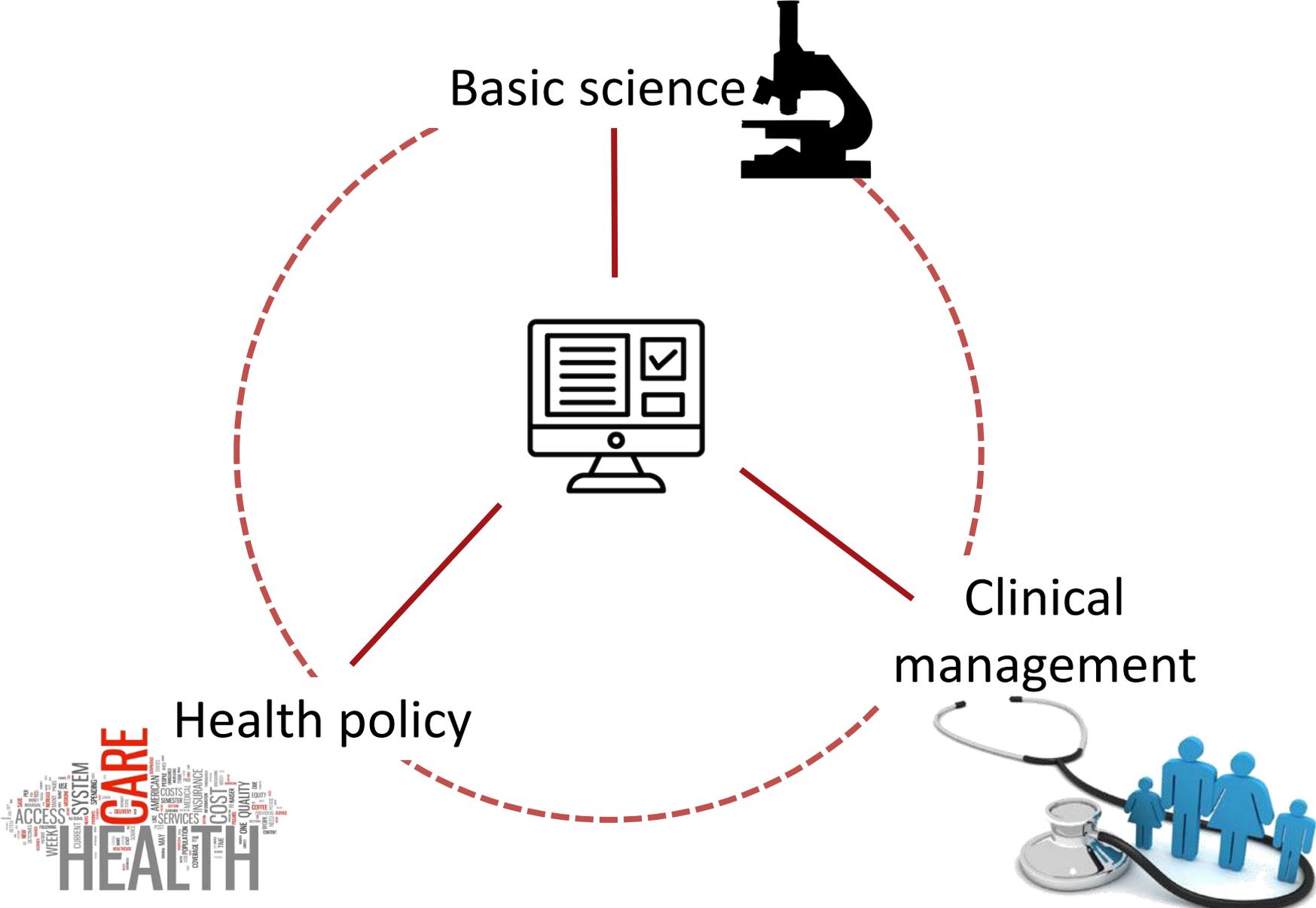
The SAFEHEART risk equation

Pérez de Isla L, et al. *Circulation.* 2017

FH registries



FH registries



Thanks