NOVETATS DIAGNÒSTIQUES EN LES CONSULTES D'ENDOCRINOLOGIA

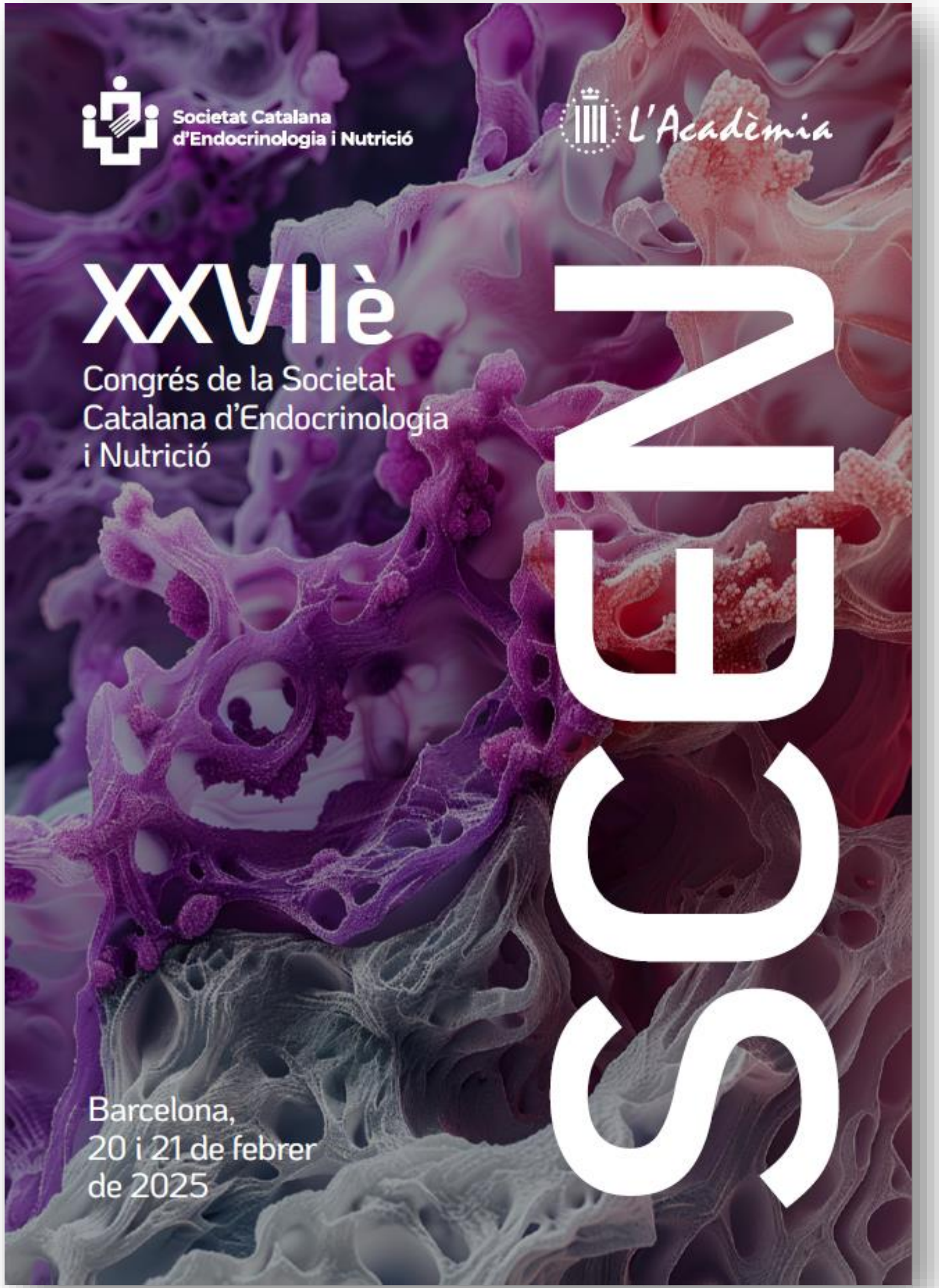
Càlcul del risc poligènic en dislipèmies

Ignacio Blanco

Laboratori Clínic Metropolitana Nord

Genètica Mèdica

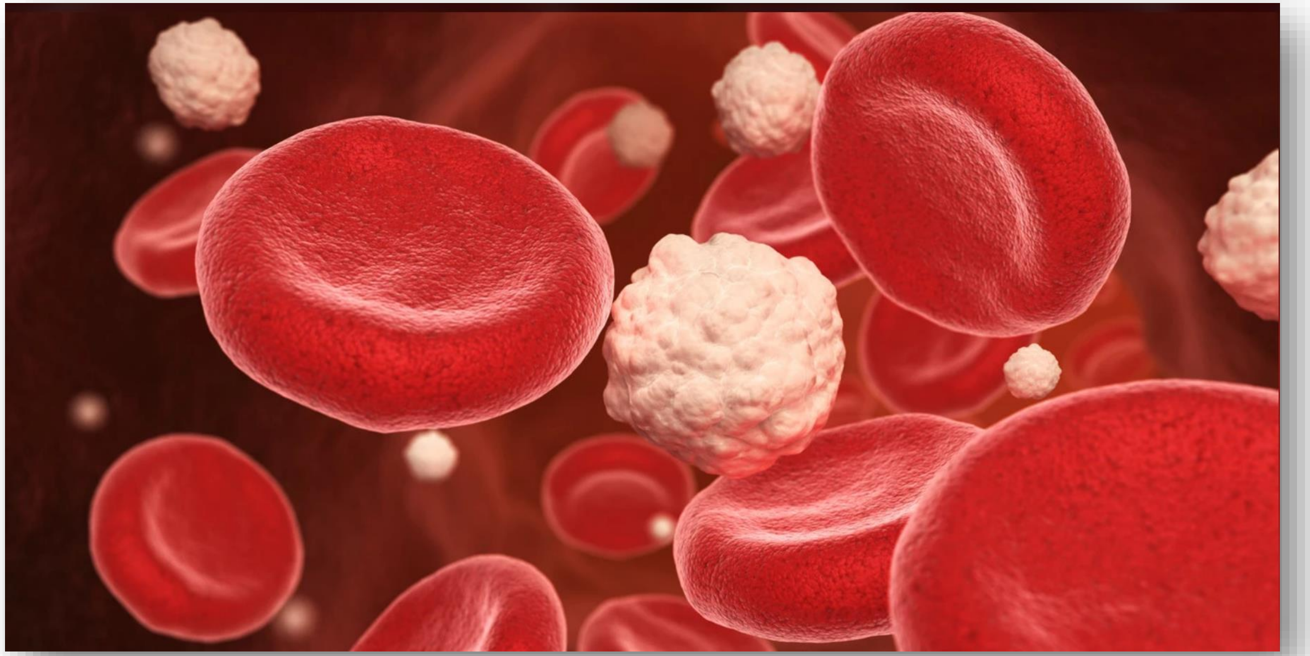
Salut/ Germans Trias i Pujol Hospital



http://imagenesgraciosas.es/paracaidista/

Dislipèmia

- **Nivells anormals** o **alterat**s de **lípids** a la sang. Es defineix com un augment dels nivells de colesterol total, lipoproteïnes de baixa densitat (LDL) i triglicèrids (TG), amb nivells disminuïts de lipoproteïnes d'alta densitat (HDL) a la sang.



https://www.vitonica.com/enfermedades/dislipemia-causas-sintomas-tratamiento

Dislipèmia

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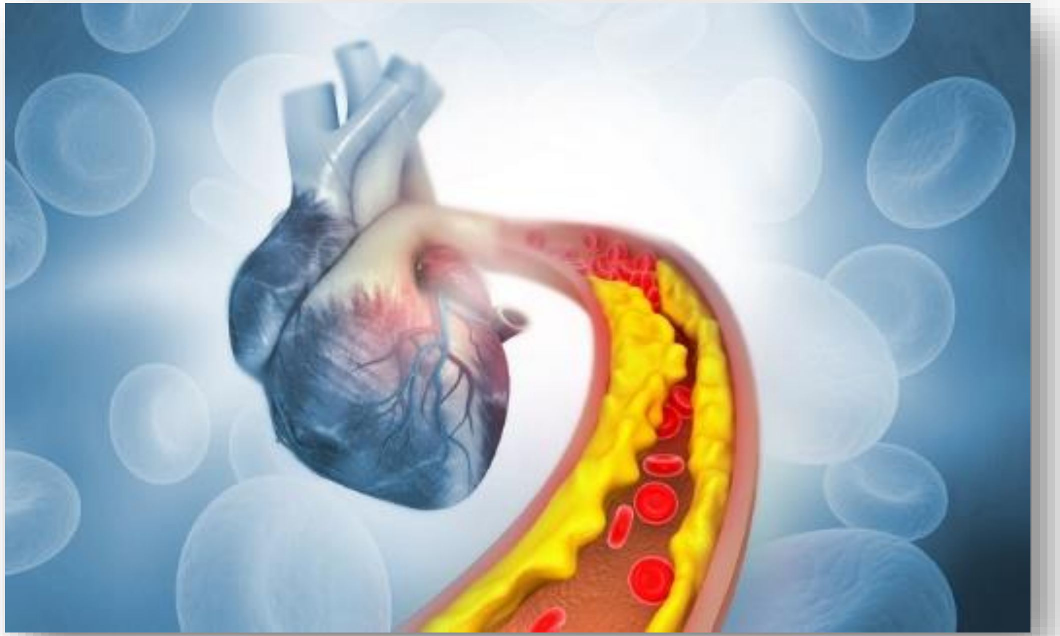
- Es el **factor de risc modificable** més important per a les **malalties cardiovasculars**, que són la causa principal de mort al món.



https://www.auladelafarmacia.com/el-seguimiento-de-la-dislipemia-debe-ser-periodico/amp/

Dislipèmia

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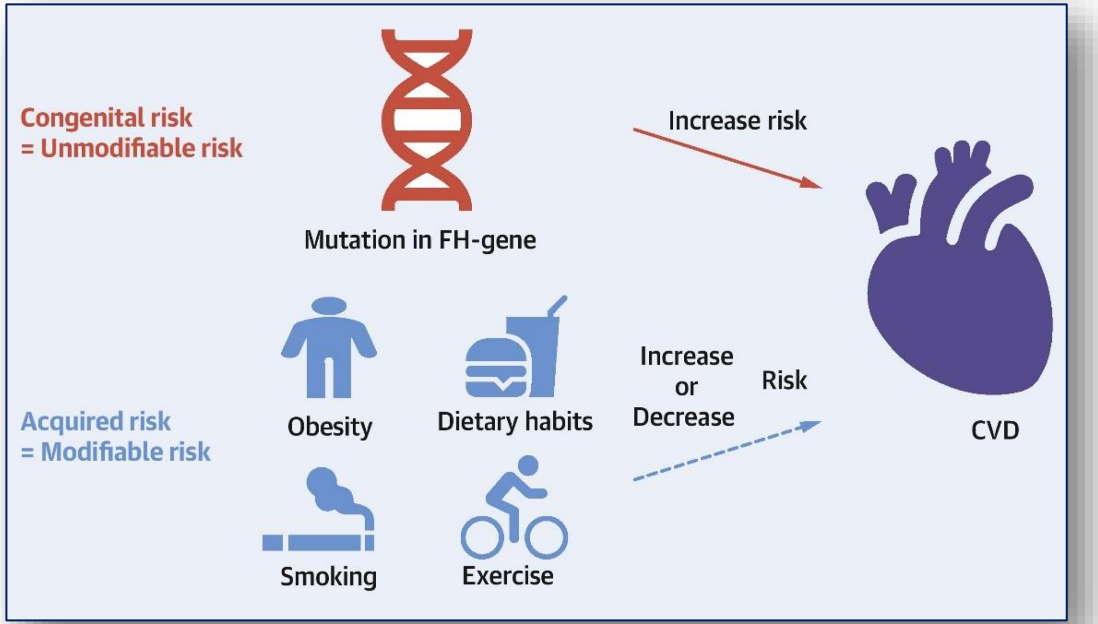
- Es el **factor de risc modificable** més important per a les **malalties cardiovasculars**, que són la causa principal de mort al món.
- La **dislipidèmia** té diverses **etiologies** influïdes per factors genètics, ambientals i d'estil de vida. Es classifica en **primària** i **secundària** segons la seva causa.



H Tada, et al. JACC: Asia 2023; 3(1): 152-160

Dislipèmia

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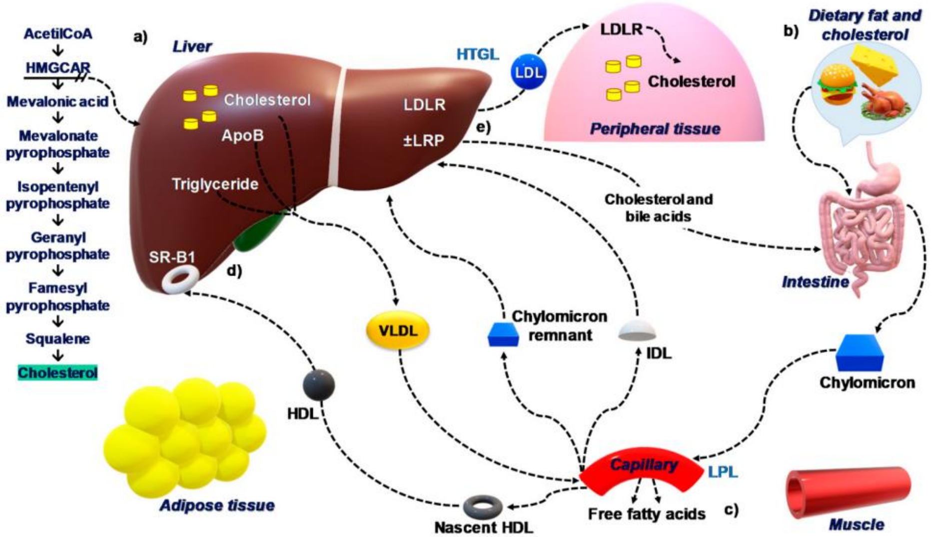
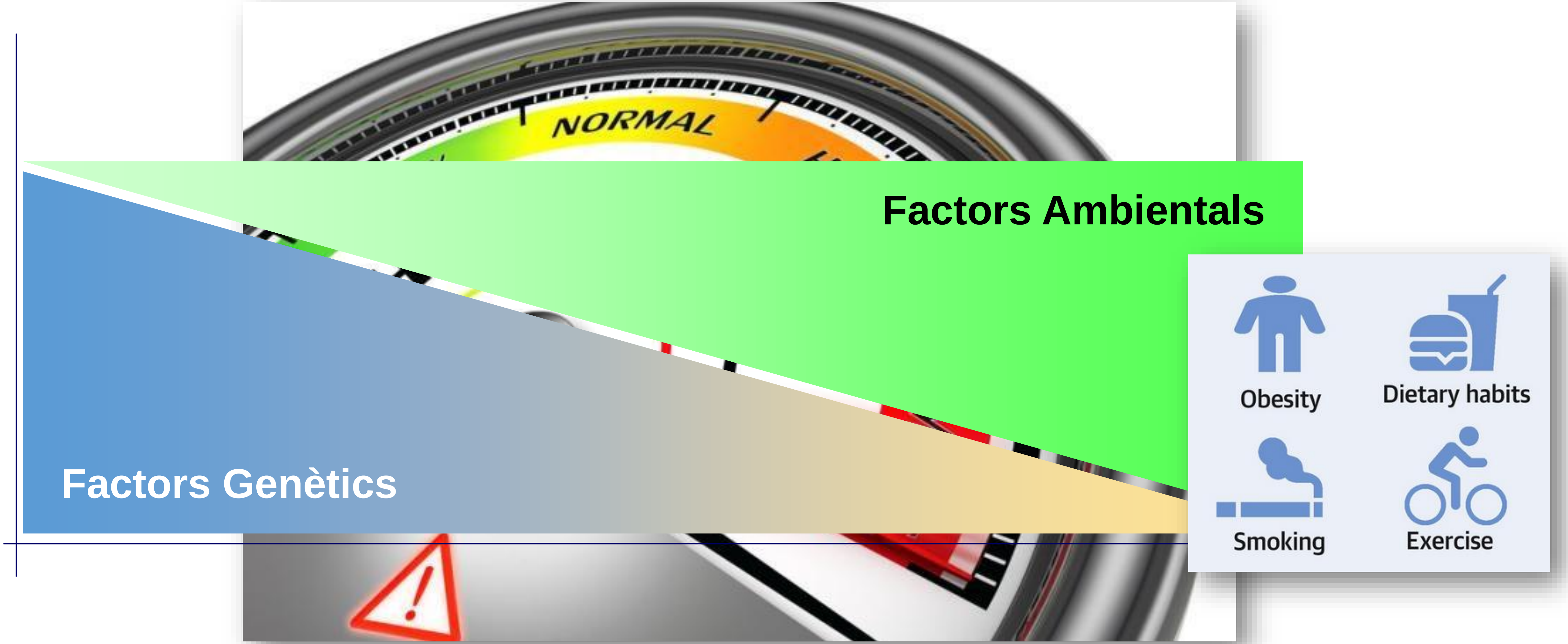
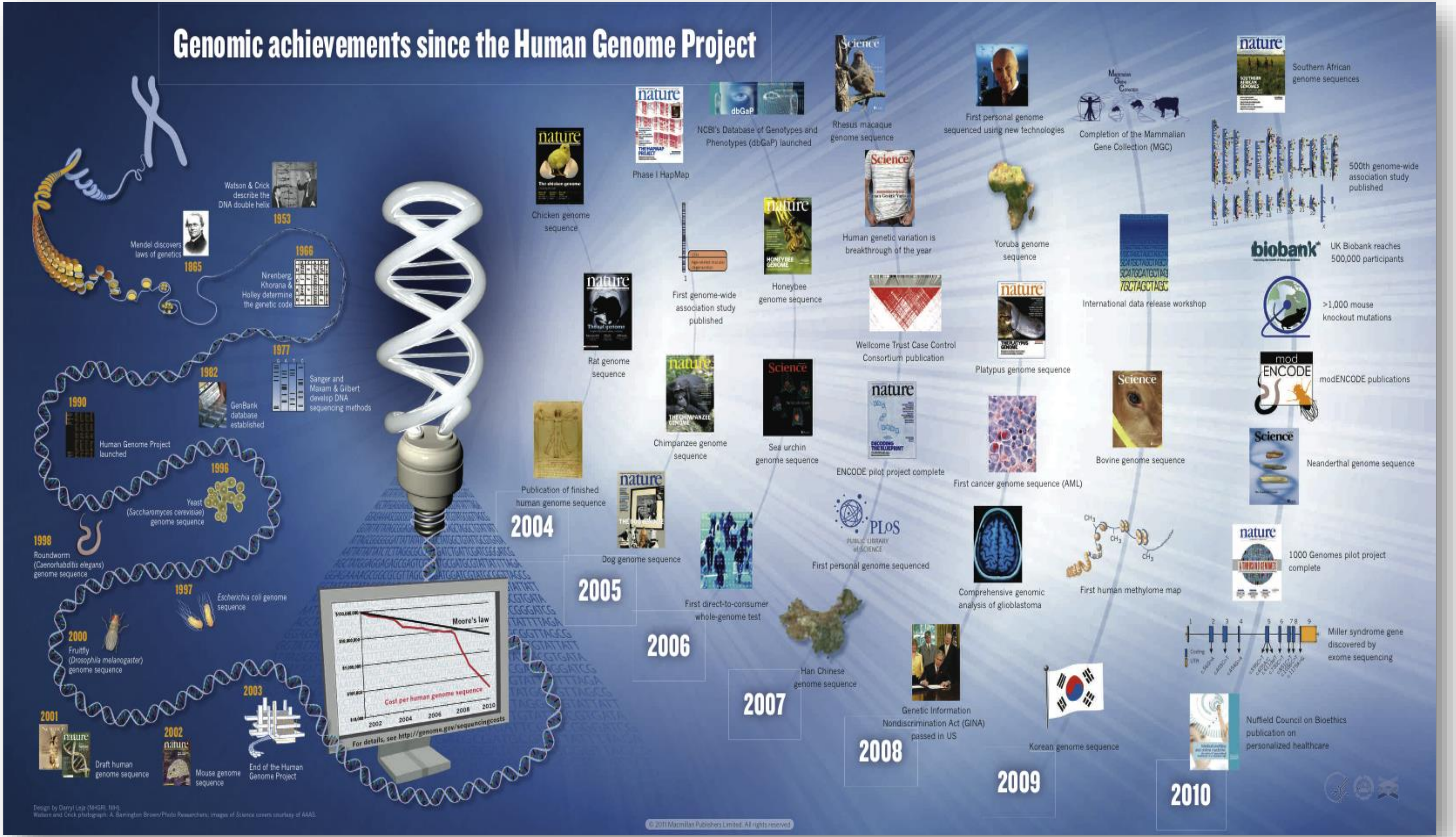
- La **dislipidèmia** té diverses **etiologies** influïdes per factors genètics, ambientals i d'estil de vida. Es classifica en **primària** i **secundària** segons la seva causa.
- La **dislipidèmia secundària** és a**dquirida** i està causada per diversos **factors externs** i de **estil de vida**. La **dislipidèmia primària** **<u>afecta</u>** el metabolisme dels lípids, mentre que la dislipidèmia secundària **<u>altera</u>** aquest metabolisme.



Dislipèmia



https://www.granalacantadvertiser.com/what-is-dyslipidemia/



ED Green et al. Nature 470, 204-213 (2011)

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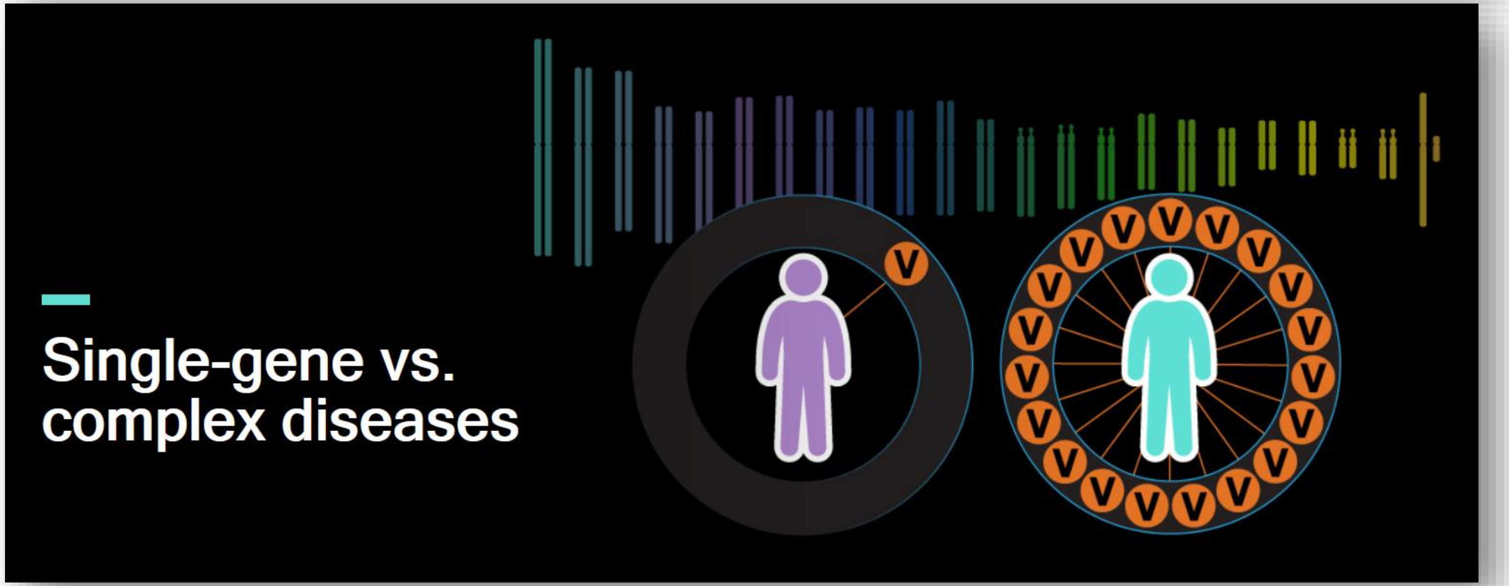
Vol 461|8 October 2009|doi:10.1038/nature08494 nature

REVIEWS

Finding the missing heritability of complex diseases

Teri A. Manolio[1], Francis S. Collins[2], Nancy J. Cox[3], David B. Goldstein[4], Lucia A. Hindorff[5], David J. Hunter[6], Mark I. McCarthy[7], Erin M. Ramos[5], Lon R. Cardon[8], Aravinda Chakravarti[9], Judy H. Cho[10], Alan E. Guttmacher[1], Augustine Kong[11], Leonid Kruglyak[12], Elaine Mardis[13], Charles N. Rotimi[14], Montgomery Slatkin[15], David Valle[9], Alice S. Whittemore[16], Michael Boehnke[17], Andrew G. Clark[18], Evan E. Eichler[19], Greg Gibson[20], Jonathan L. Haines[21], Trudy F. C. Mackay[22], Steven A. McCarroll[23] & Peter M. Visscher[24]



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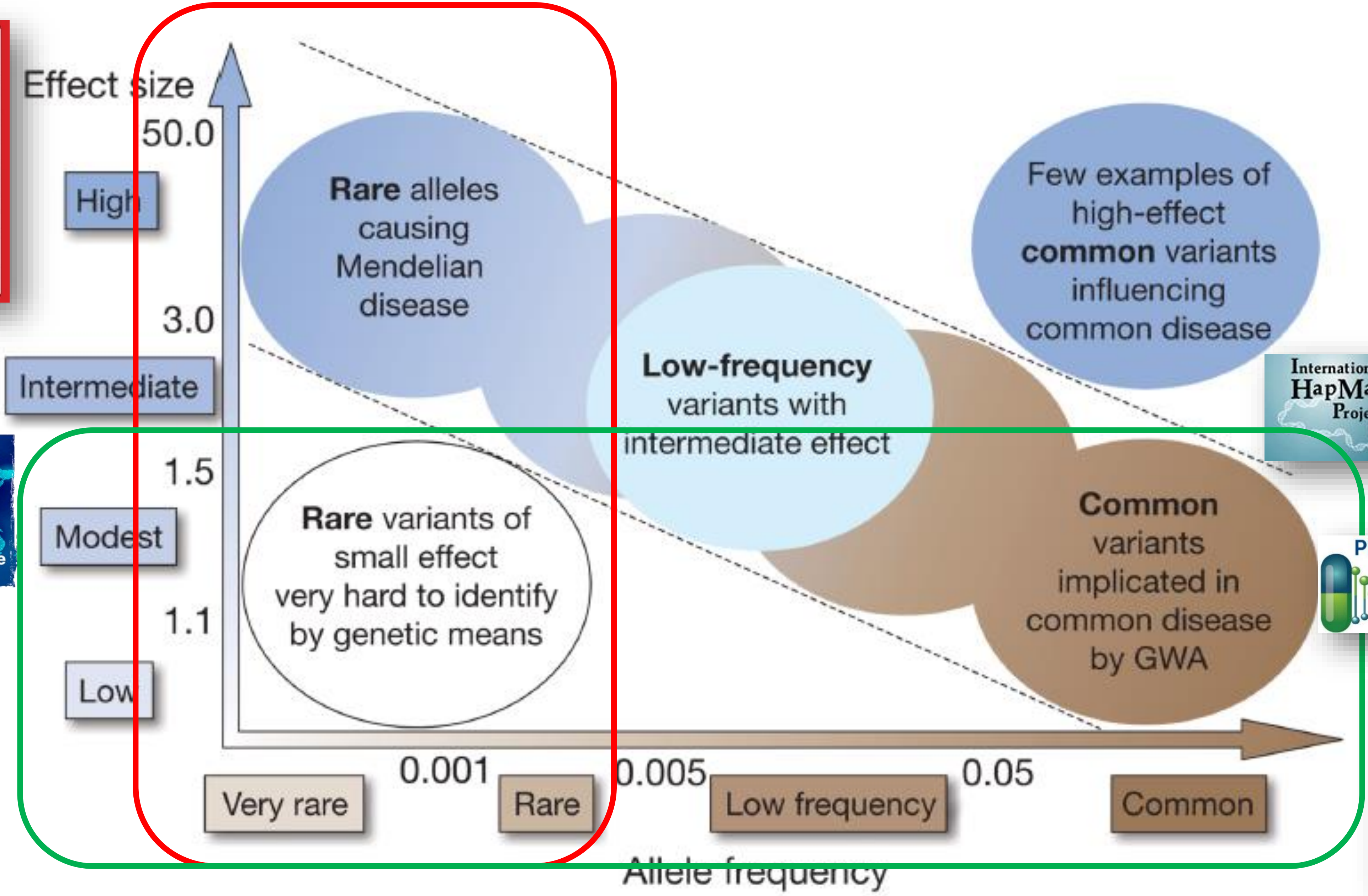
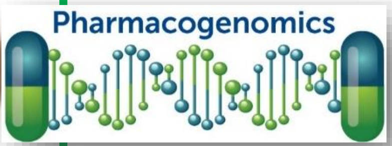
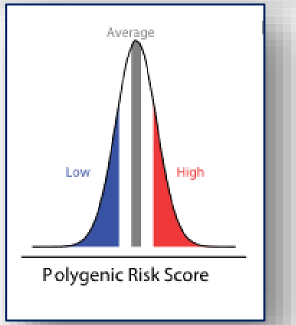
SOCIETAT CATALANA D'ENDOCRINOLOGIA I NUTRICIÓ

L'Acadèmia

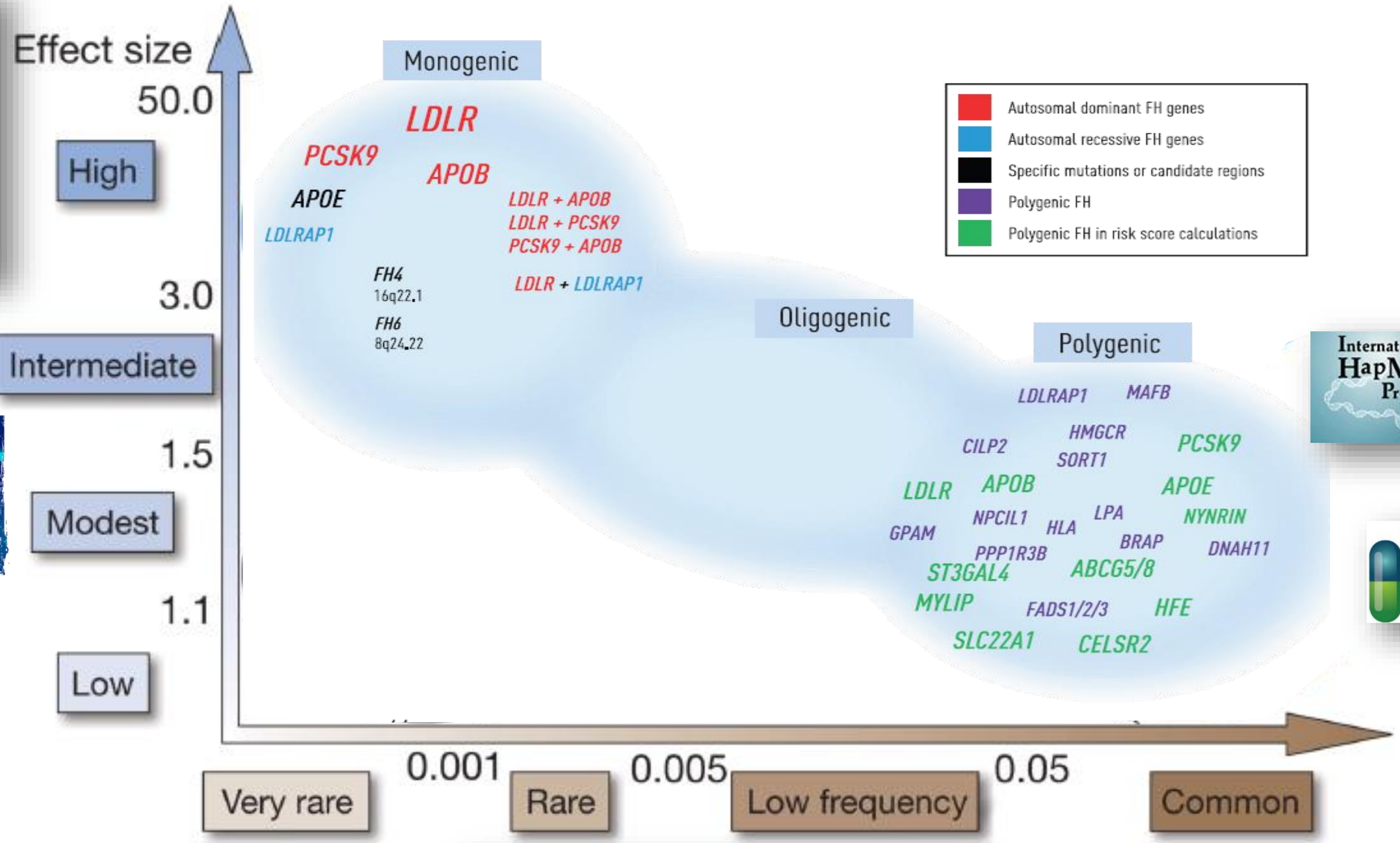


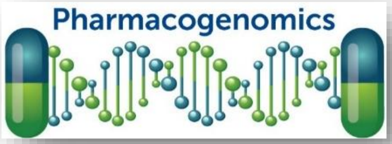


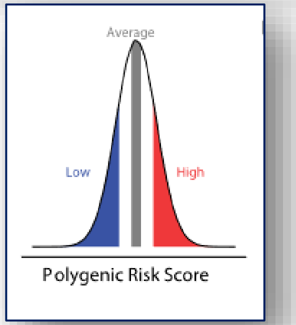


Finding the missing heritability of complex diseases

Manolio TA, et al. Nature. 2009 Oct 8; 461(7265): 747–753







JIM Review
doi: 10.1111/joim.13577

Genetic and molecular architecture of familial hypercholesterolemia

Marianne Abifadel[1,2] & Catherine Boileau[1,3]

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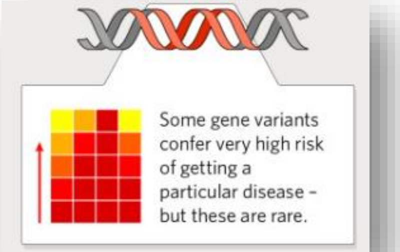
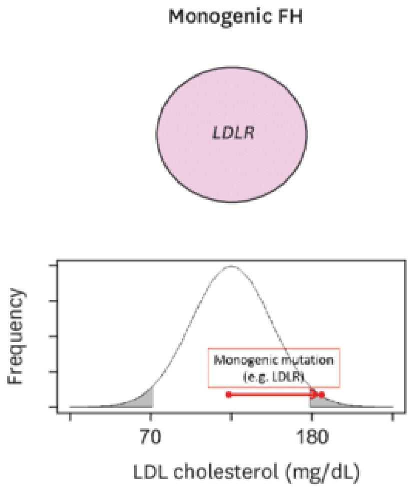
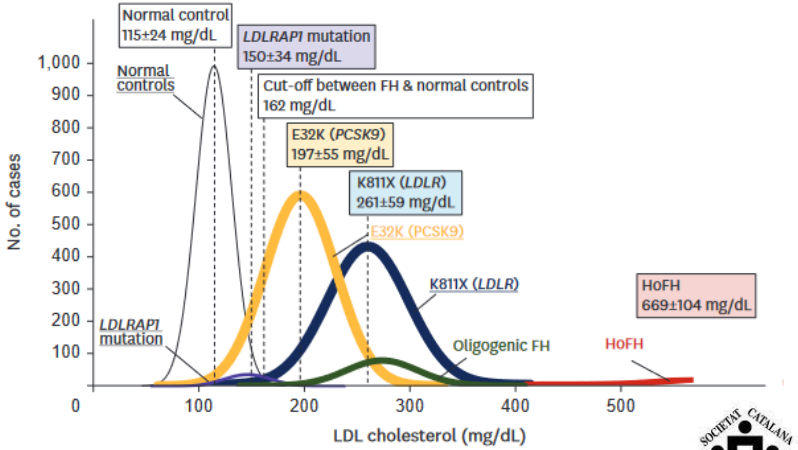
Societat Catalana d'Endocrinologia i Nutrició

L'Acadèmia



Gene	Protein	Chromosomal location (number of exons)	MIM number(s)	Number of mutations*
Autosomal co-dominant inheritance‡				
LDLR	LDL receptor	19p13.2 (18)	143890, 606945	>2,000
APOB	Apolipoprotein B100	2p24.1 (29)	144010, 107730	32
PCSK9	Proprotein convertase subtilisin/kexin type 9	1p32.3 (13)	603776, 607786	23
Autosomal dominant inheritance				
APOE	Apolipoprotein E	19q13.32 (6)	107741	1
STAP1	Signal-transducing adaptor protein 1	4q13.2 (10)	604298	4
Recessive inheritance				
LDLRAP1	LDL receptor adaptor protein 1	1p36.11 (15)	603813, 605747	17
ABCG5	Sterolin 1	2p21 (15)	210250, 605459	2
ABCG8	Sterolin 2	2p21 (14)		
LIPA	Lysosomal acid lipase	10q23.31 (10)	278000, 613497	1





Tada H, et al. J Lipid Atheroscler. 2022 Jan;11(1):39-54

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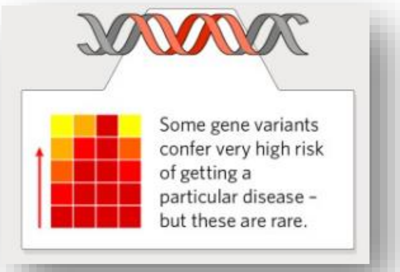
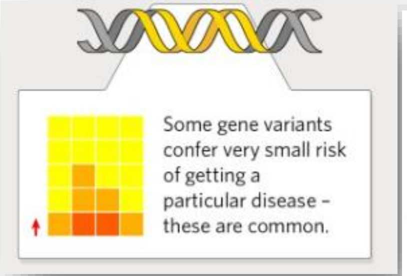
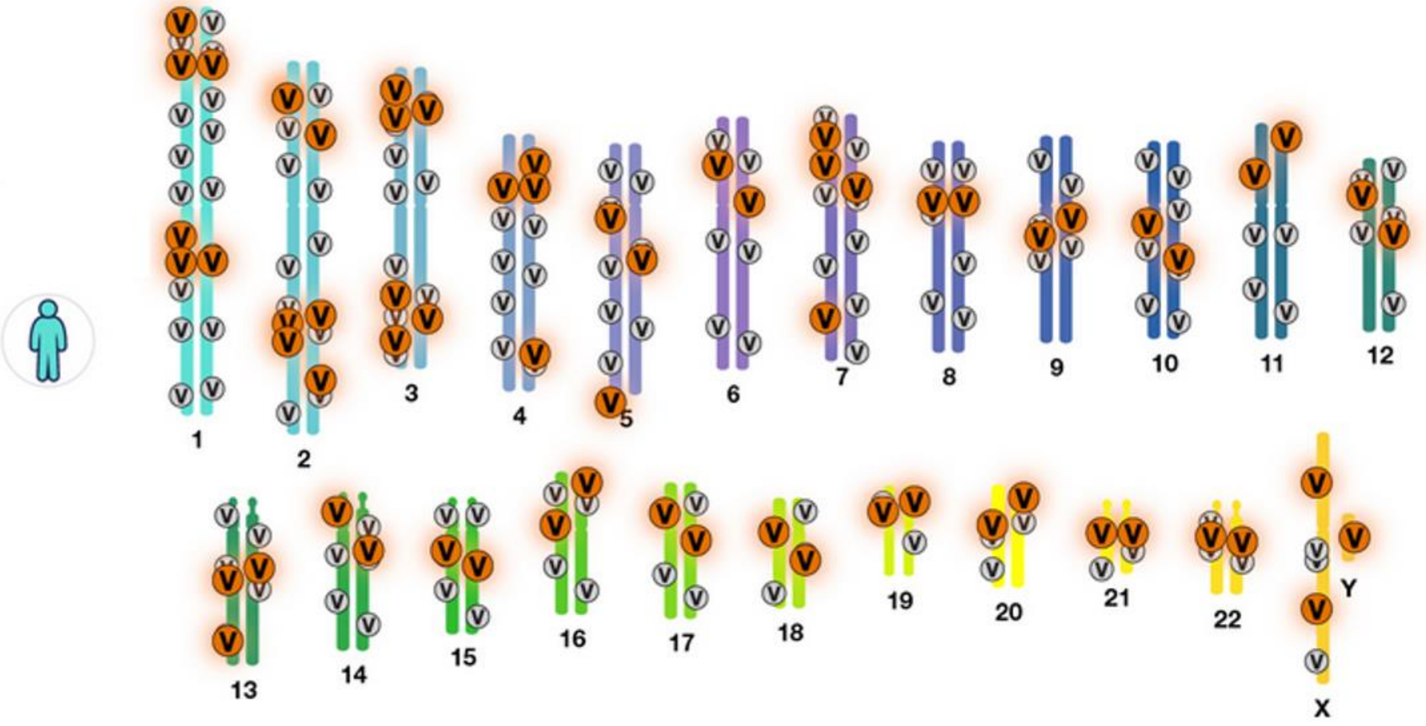
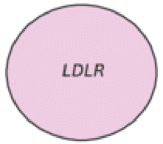




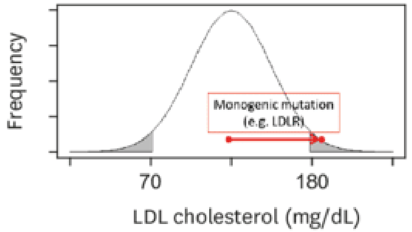


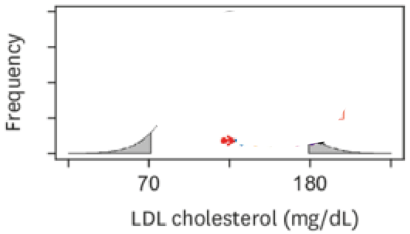
Monogenic FH



$$PRS = \sum SNP_i \cdot \beta_i$$

Polygenic FH





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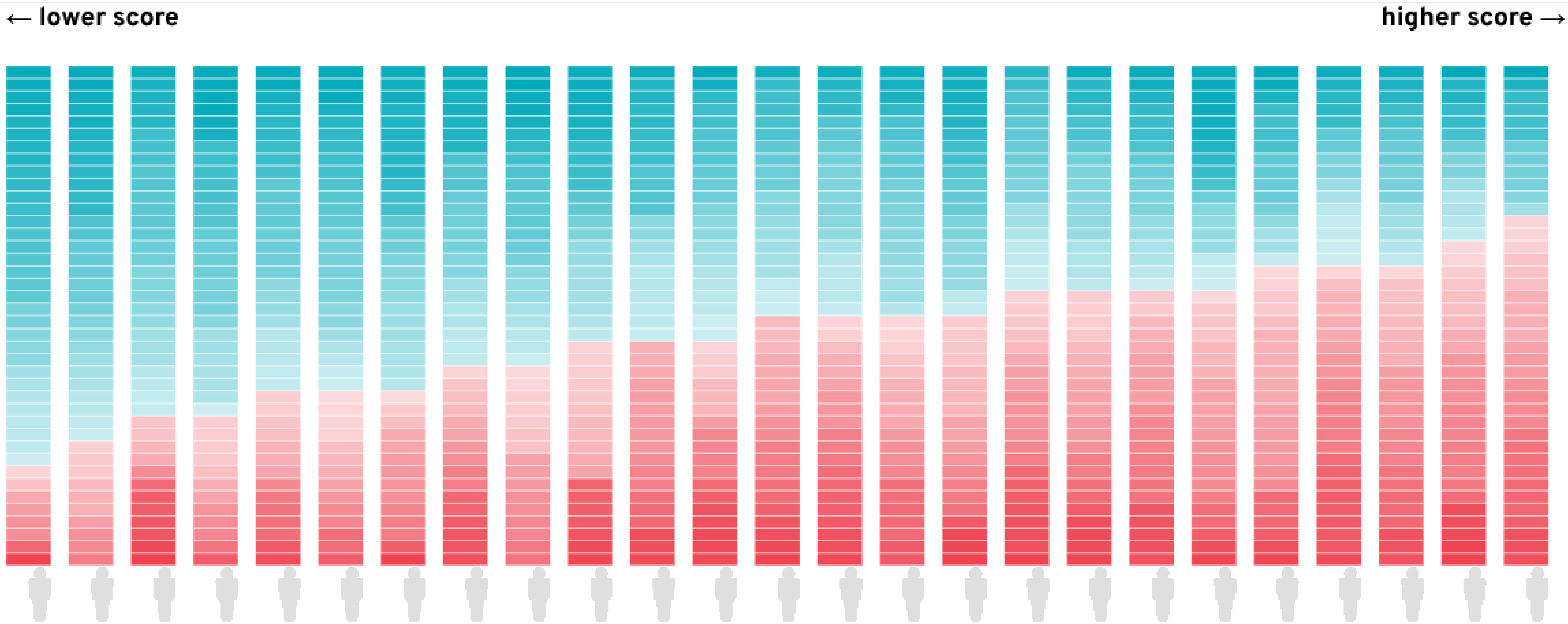
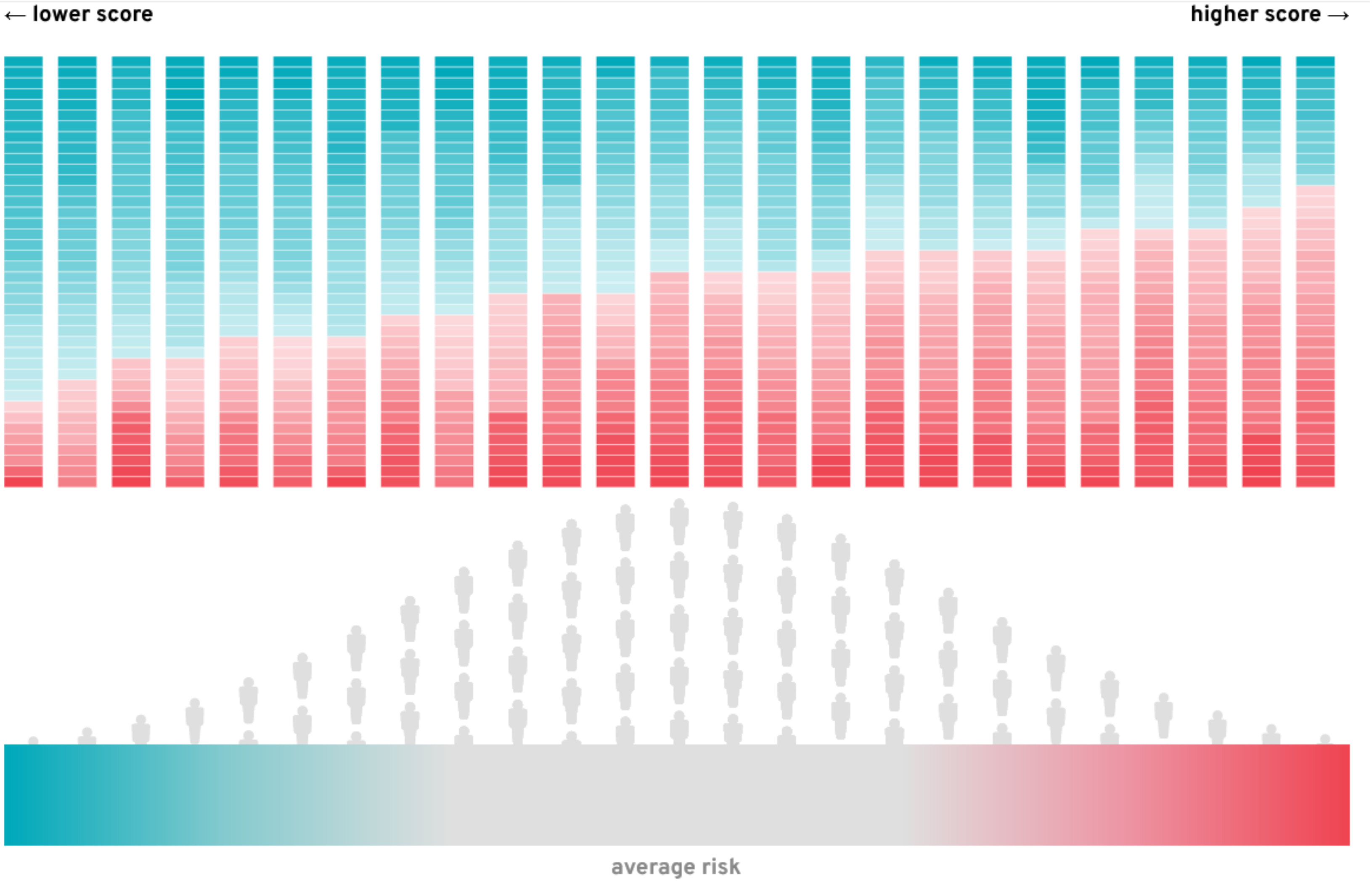
SOCIETAT CATALANA D'ENDOCRINOLOGIA I NUTRICIÓ

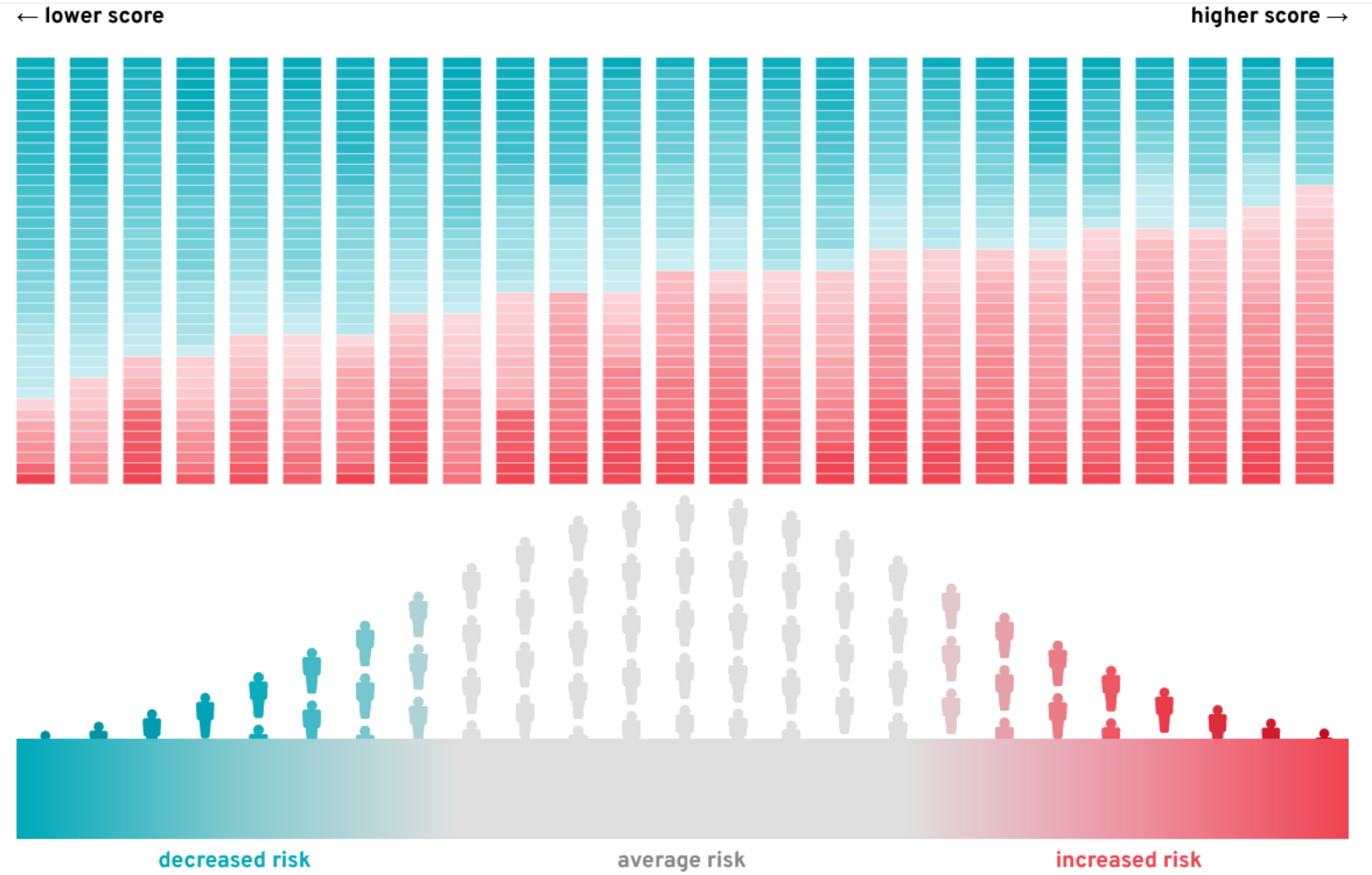
L'Acadèmia FUNDACIÓ ACADÈMIA DE CIÈNCIES MÈDIQUES I DE LA SALUT DE CATALUNYA I DE BALEARS

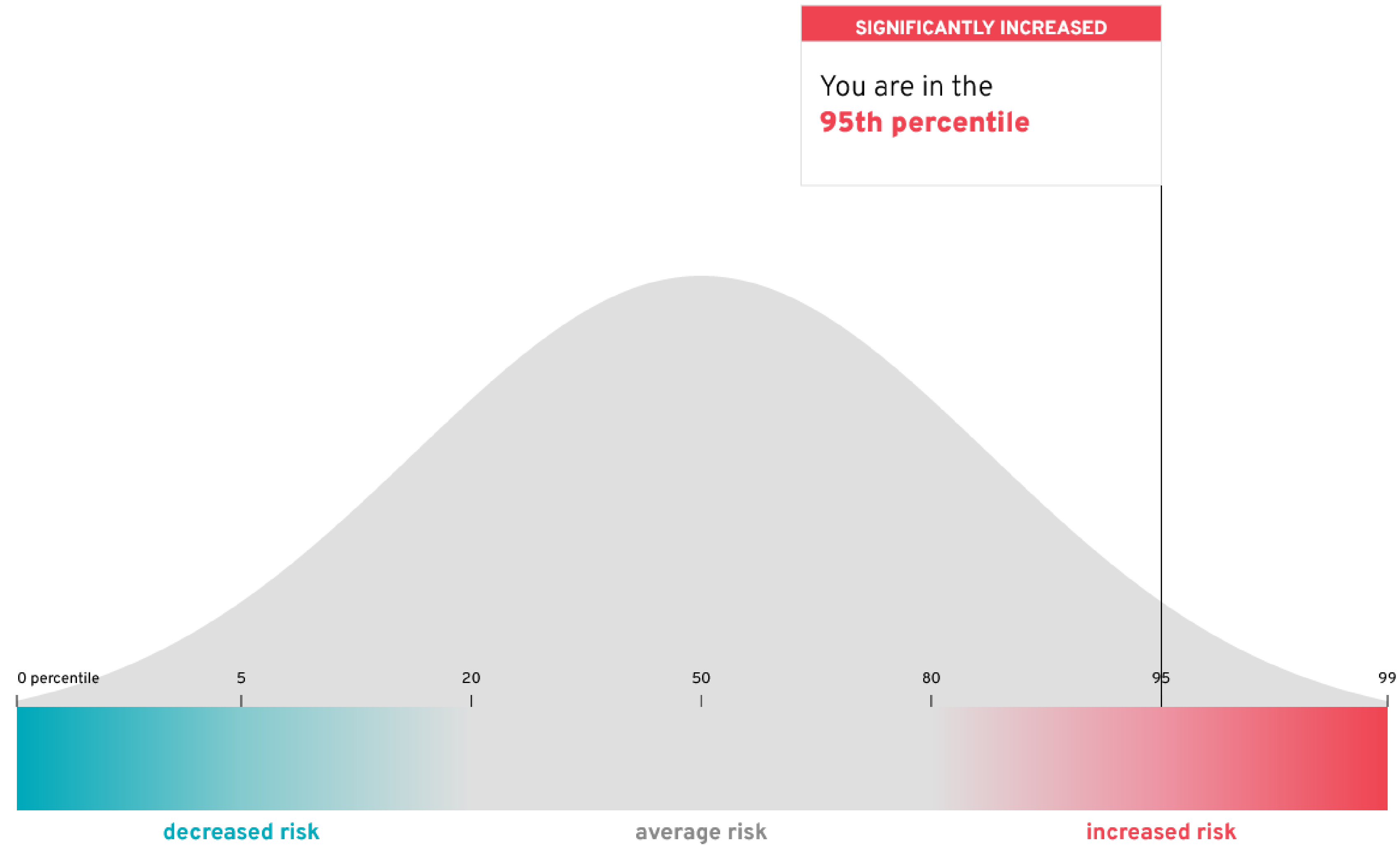


← lower score
higher score →



← lower score
higher score →
average risk


← lower score
higher score →
decreased risk
average risk
increased risk



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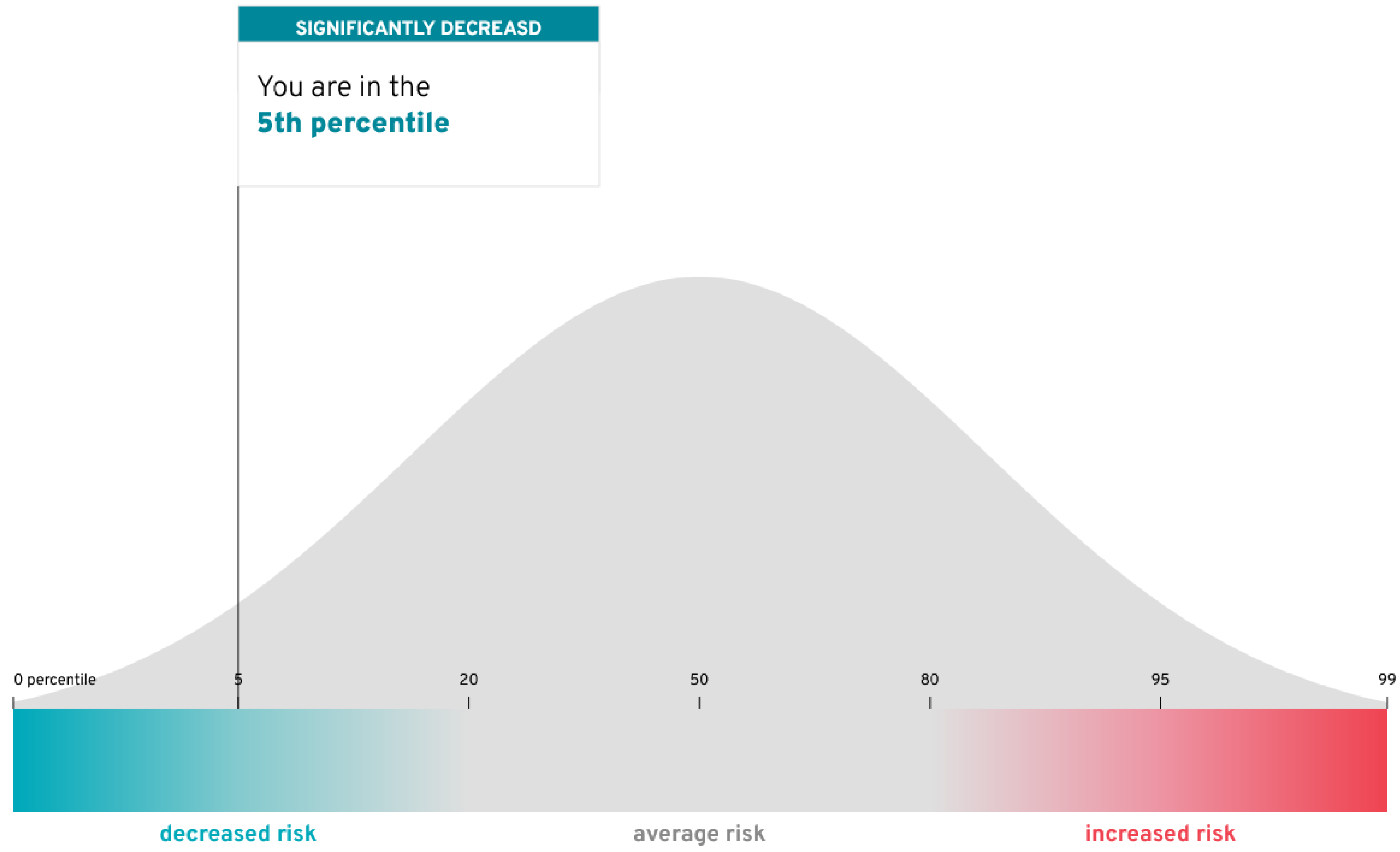
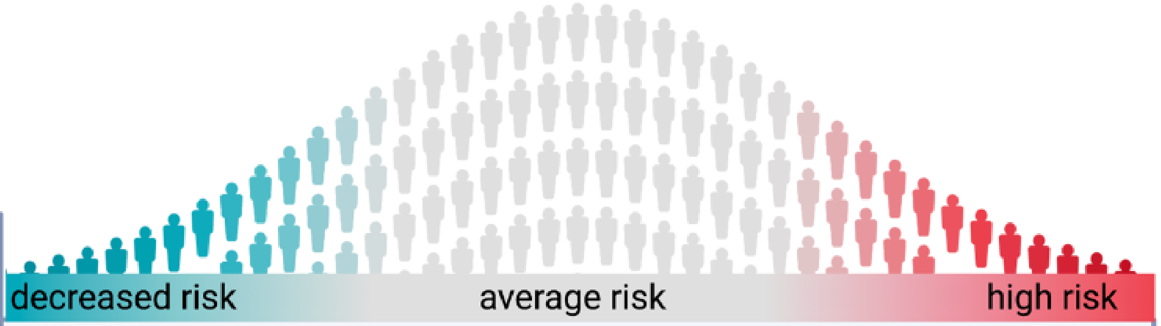
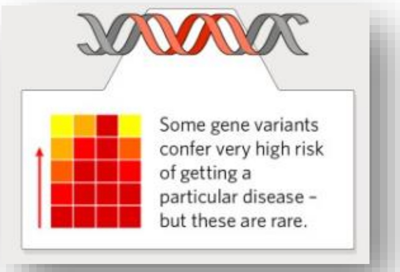


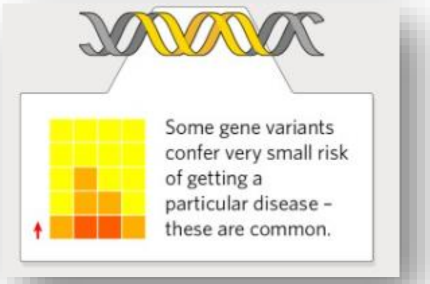
Germans Trias i Pujol
Hospital

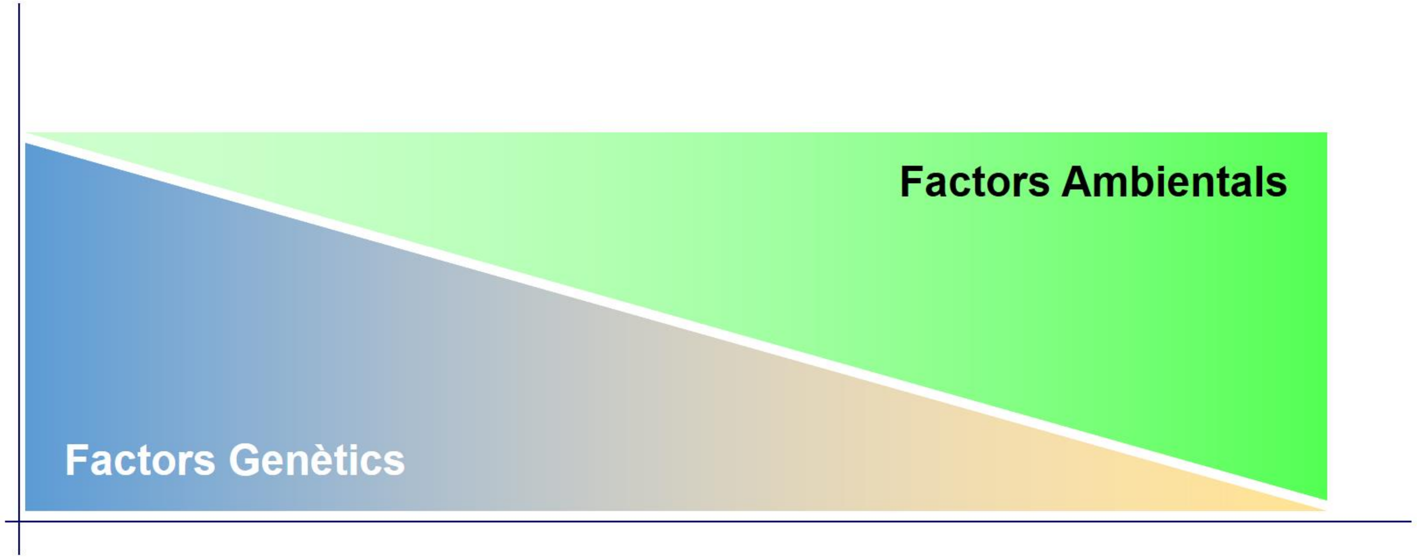
Polygenic Risk Score Distribution



Use Cases for Providers			
Clinical decision making, particularly when little personalized information is available	Useful when below threshold		Useful when above threshold
Encouraging patients to do what has already been recommended by their provider	Concern patients will dismiss recommendations		Result may urge patient to follow recommendations
Identifying previously unrecognized high risk patients that were missed by traditional risk assessment			Useful for patients missed by traditional factors


Some gene variants
confer very high risk
of getting a
particular disease -
but these are rare.


Some gene variants
confer very small risk
of getting a
particular disease -
these are common.


Factors Ambientals
Factors Genètics

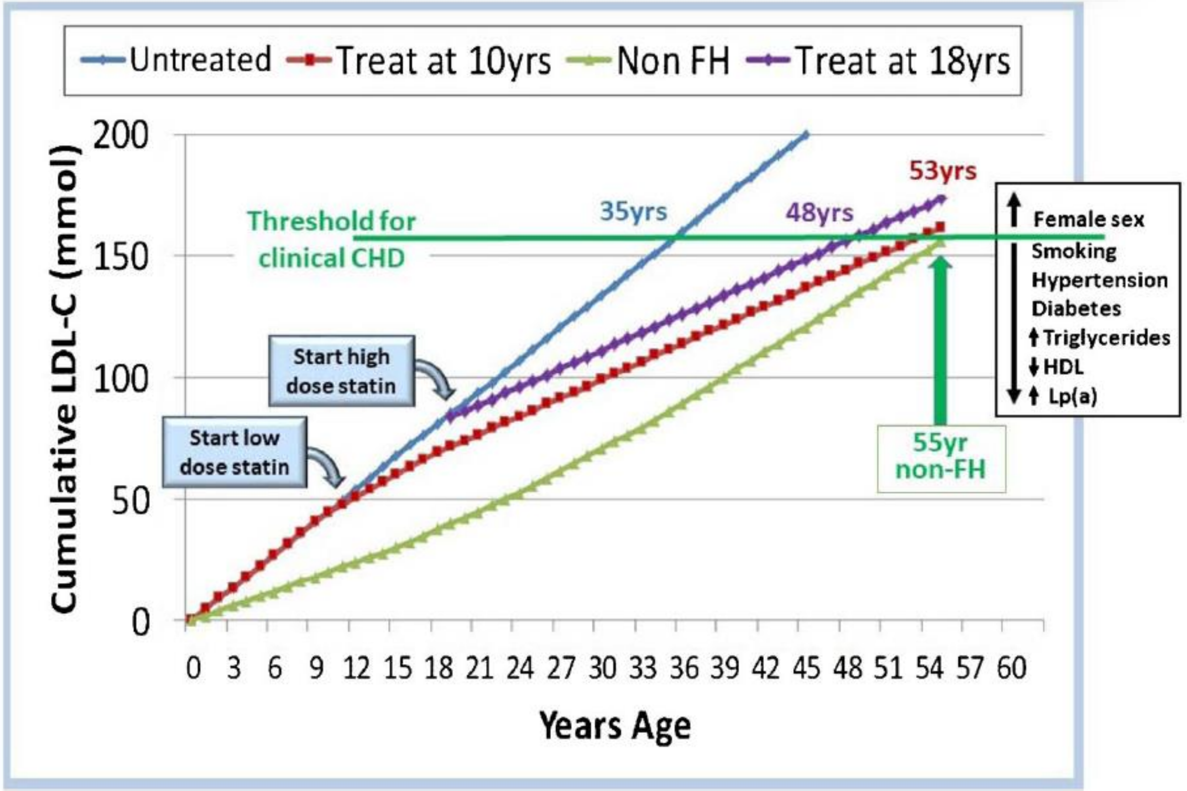
Current Cardiology Reports (2019) 21: 43
https://doi.org/10.1007/s11886-019-1130-z

LIPID ABNORMALITIES AND CARDIOVASCULAR PREVENTION (G DE BACKER, SECTION EDITOR)

Check for updates

Polygenic Hypercholesterolemia and Cardiovascular Disease Risk

Mahtab Sharifi[1,2] · Marta Futema[1] · Devaki Nair[2] · Steve E. Humphries[1]



https://gfycat.com/idolizedoffbeatgreendarnerdragonfly

https://www.nature.com/articles/d42473-019-00270-w

Atherosclerosis 277 (2018) 457–463

Contents lists available at ScienceDirect

Atherosclerosis

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

Review article

Clinical utility of the polygenic LDL-C SNP score in familial hypercholesterolemia

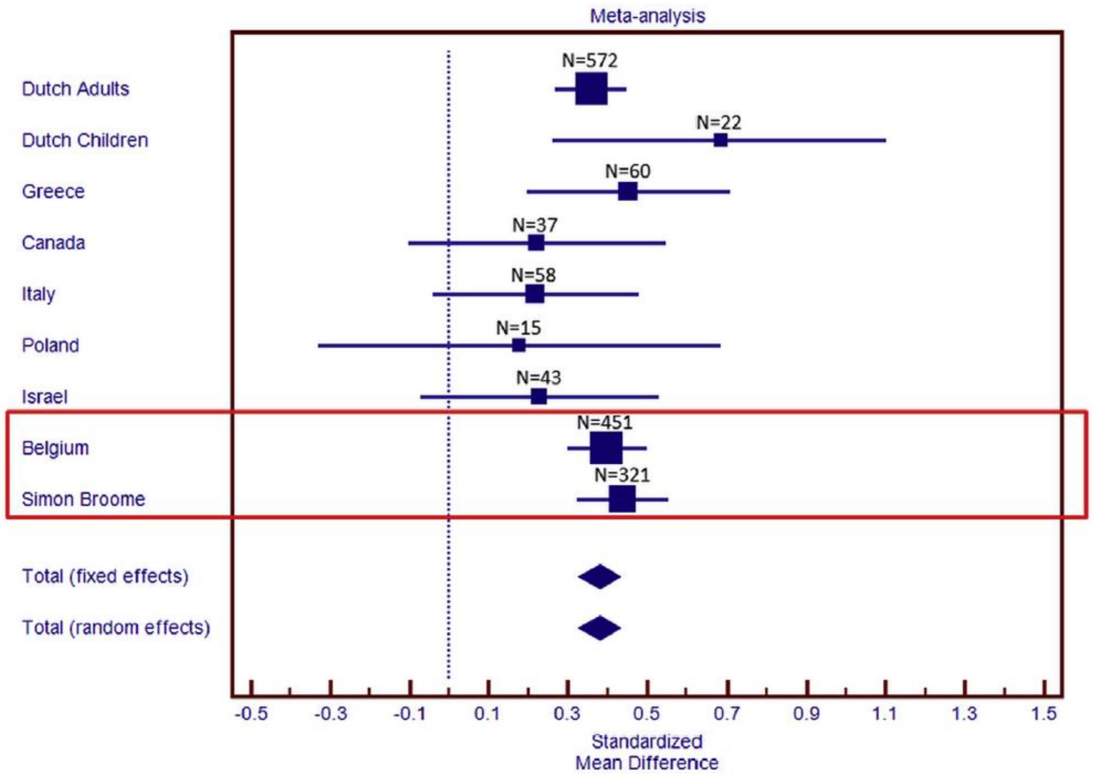
Marta Futema [a], Mafalda Bourbon [b, c], Maggie Williams [d], Steve E. Humphries [e, *]

Global Lipid Genetic Consortium [10] 12 SNP LDL-C Gene Score, showing the LDL-C-raising allele and the published raising effect (in mmol/l).

CHR	SNP	Gene	Minor[a]	Common[a]	GLGC weight
1	rs2479409	*PCSK9*	**G**	A	0.052
1	**rs629301**	***CELSR2***	G	**T**	0.15
2	**rs1367117**	***APOB***	**A**	G	0.10
2	**rs4299376**	***ABCG8***	**G**	T	0.071
6	rs1564348	*SLC22A1*	C	**T**	0.014
6	rs1800562	*HFE*	A	**G**	0.057
6	rs3757354	*MYLIP*	T	**C**	0.037
11	rs11220462	*ST3GAL4*	**A**	G	0.050
14	rs8017377	*KIAA1305*	**A**	G	0.029
19	**rs6511720**	***LDL-R***	T	**G**	0.18
19	**rs429358**	***APOE***	C	T	
19	**rs7412**	***APOE***	T	C	
		ε2ε2			−0.9
		ε2ε3			−0.4
		ε2ε4			−0.2
		ε3ε3			0
		ε3ε4			0.1
		ε4ε4			0.2

GLGC weights from Ref. [10] and *APOE* weights were based on haplotypic effects taken from [42].

[a] Risk alleles (LDL-C-raising) are indicated in bold. rs numbers and gene symbols in bold indicate the 6-SNPs used in [15].



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Current Cardiology Reports (2022) 24:1669–1677
https://doi.org/10.1007/s11886-022-01783-5

LIPID ABNORMALITIES AND CARDIOVASCULAR PREVENTION (ED MICHOS, SECTION EDITOR)

Check for updates

The Clinical Importance of Differentiating Monogenic Familial Hypercholesterolemia from Polygenic Hypercholesterolemia

Fistra Janrio Tandirerung[1]

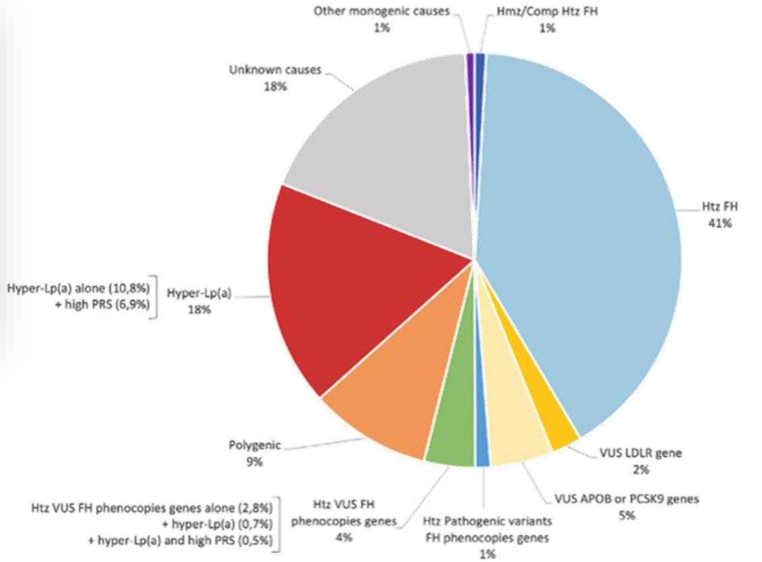
- **Monogenic FH** patients are at **higher risk** for CHD with **poorer therapeutic response**.
- Thus, genotype testing **should be performed** when available.
- There is also an urgency to develop **genotype-based clinical guideline** that stratify patients on genotype and not only based on traditionally known cardiovascular risk factors.

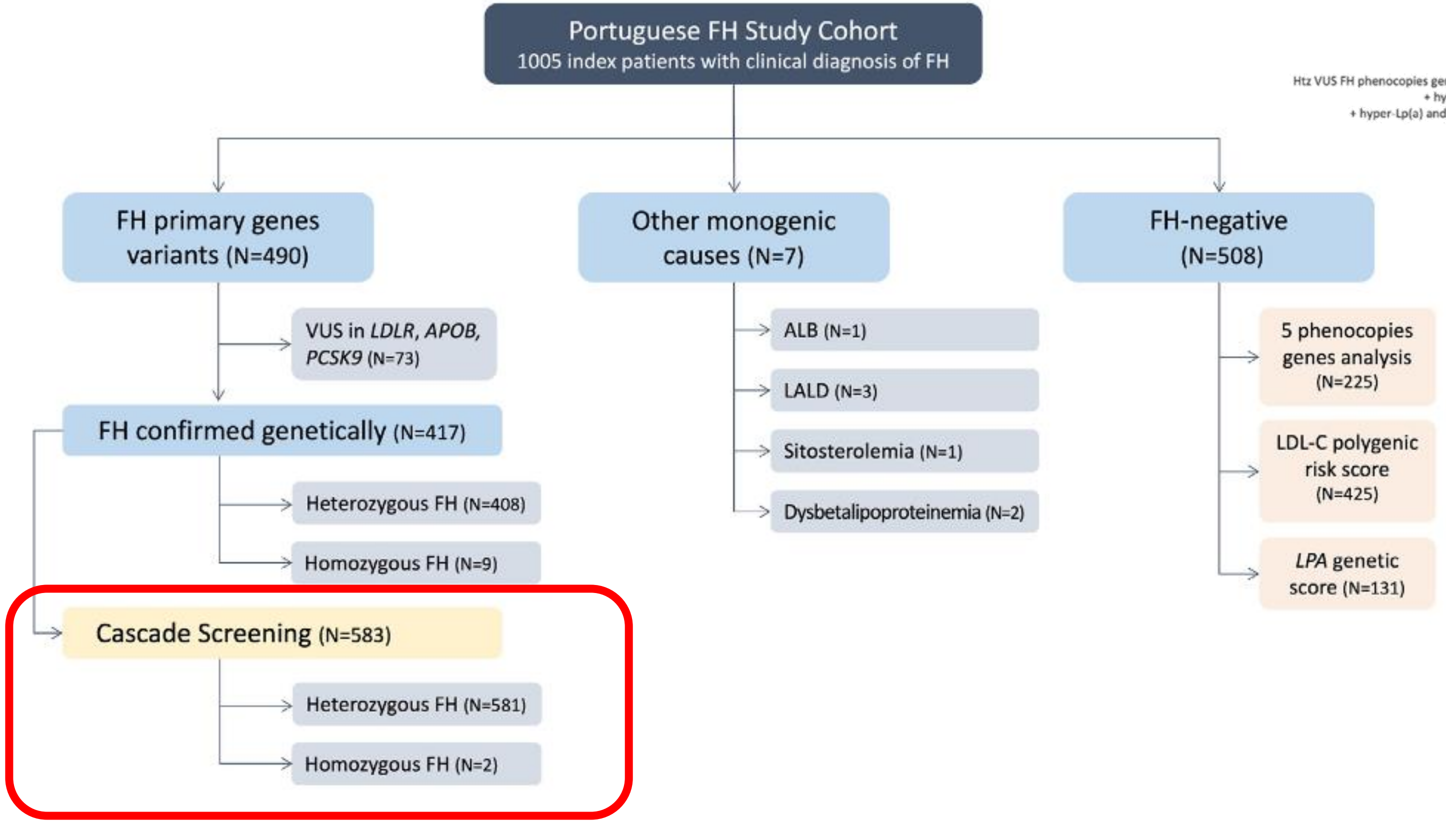
JLR RESEARCH ARTICLE

J. Lipid Res. (2024) 65(2) 100490

Unraveling the genetic background of individuals with a clinical familial hypercholesterolemia phenotype

Ana Margarida Medeiros[1,2], Ana Catarina Alves[1,2], Beatriz Miranda[1,2], Joana Rita Chora[1,2], and Mafalda Bourbon[1,2,*] on behalf of the investigators of the Portuguese FH Study[‡]





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Societat Catalana d'Endocrinologia i Nutrició

L'Acadèmia Fundació Acadèmia de Ciències Mèdiques i de la Salut de Catalunya i de Balears

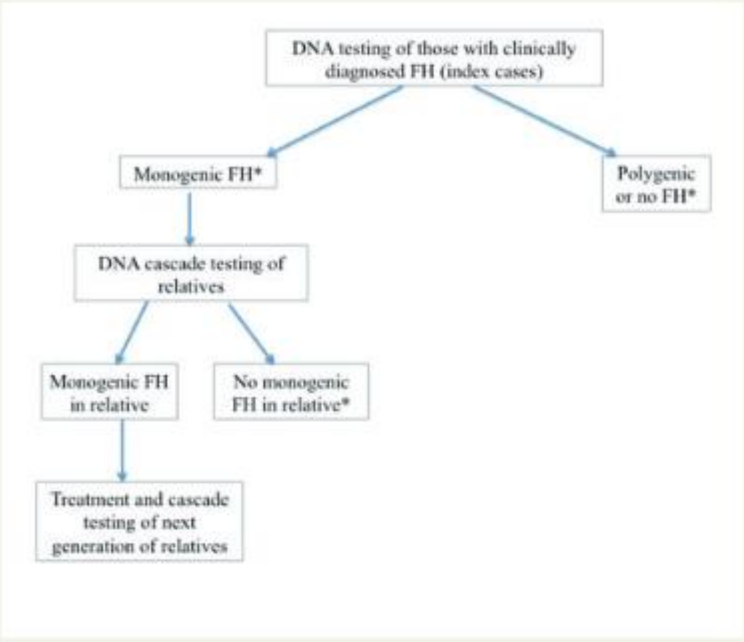
EUROPEAN SOCIETY OF CARDIOLOGY®

European Heart Journal (2017) **38**, 1832–1839
doi:10.1093/eurheartj/ehx111

CLINICAL RESEARCH
Prevention and epidemiology

Cost effectiveness of cascade testing for familial hypercholesterolaemia, based on data from familial hypercholesterolaemia services in the UK

Marion Kerr[1], Robert Pears[2], Zofia Miedzybrodzka[3], Kate Haralambos[4], Moyra Cather[5], Melanie Watson[6], and Steve E. Humphries[7]*



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Societat Catalana d'Endocrinologia i Nutrició

L'Acadèmia

Monogenic Disorder

Variance in **one** particular gene only

Polygenic Disorder

Variance in **multiple** genes at the same time

Mendelian Inheritance

Autosomal co-dominant

Autosomal dominant

Autosomal recessive

Non-mendelian Inheritance

Atherosclerosis 277 (2018) 457–463

Contents lists available at ScienceDirect

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ELSEVIER

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Clinical utility of the polygenic LDL-C SNP score in familial hypercholesterolemia

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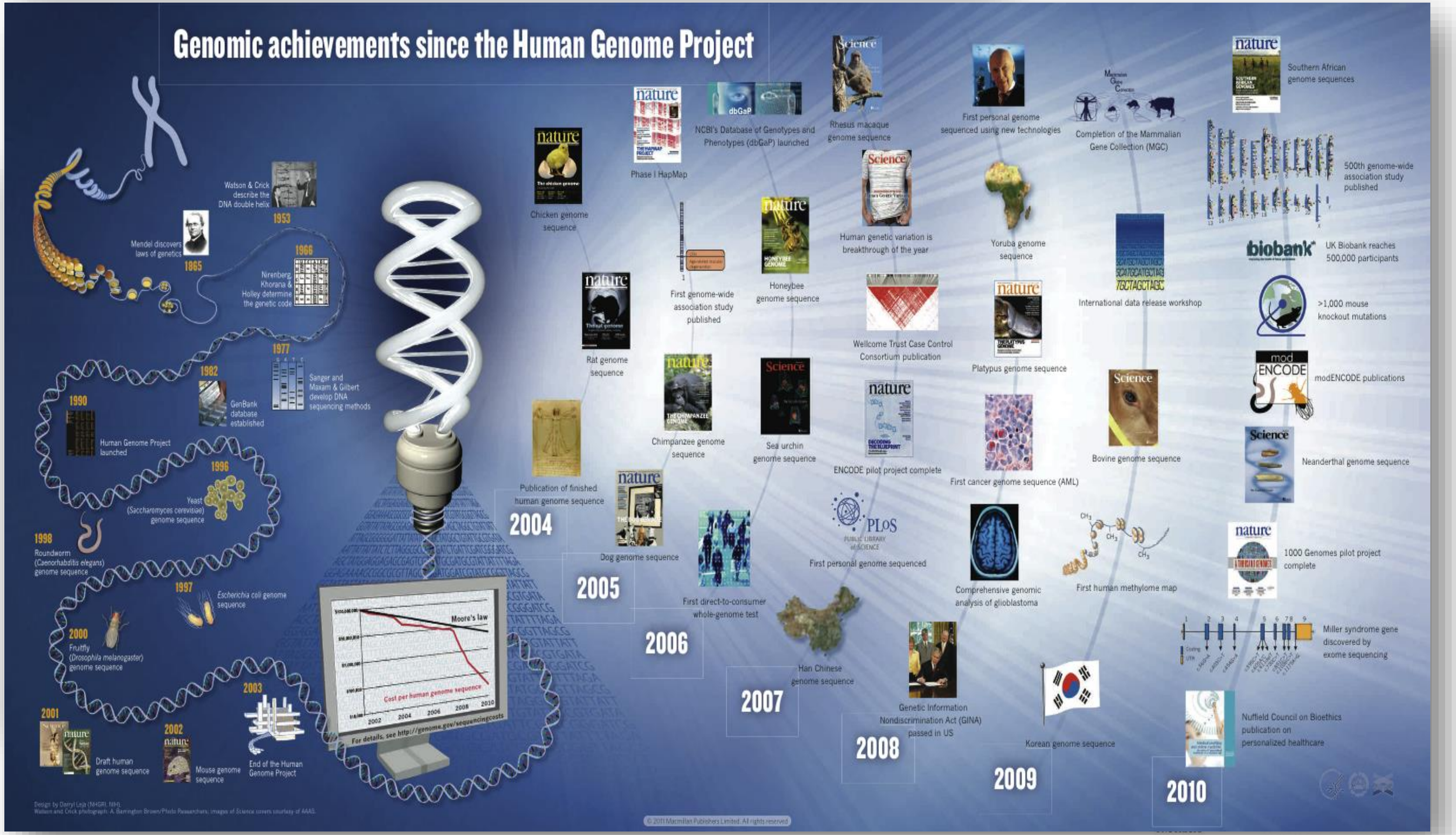

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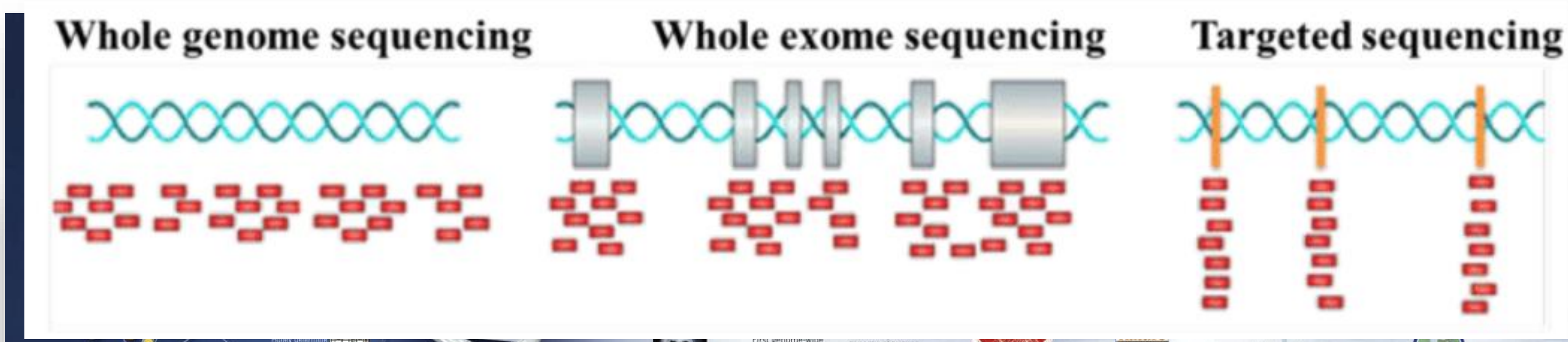
SPECIAL SECTION HUMAN GENOMICS

REVIEW

Discovery and implications of polygenicity of common diseases

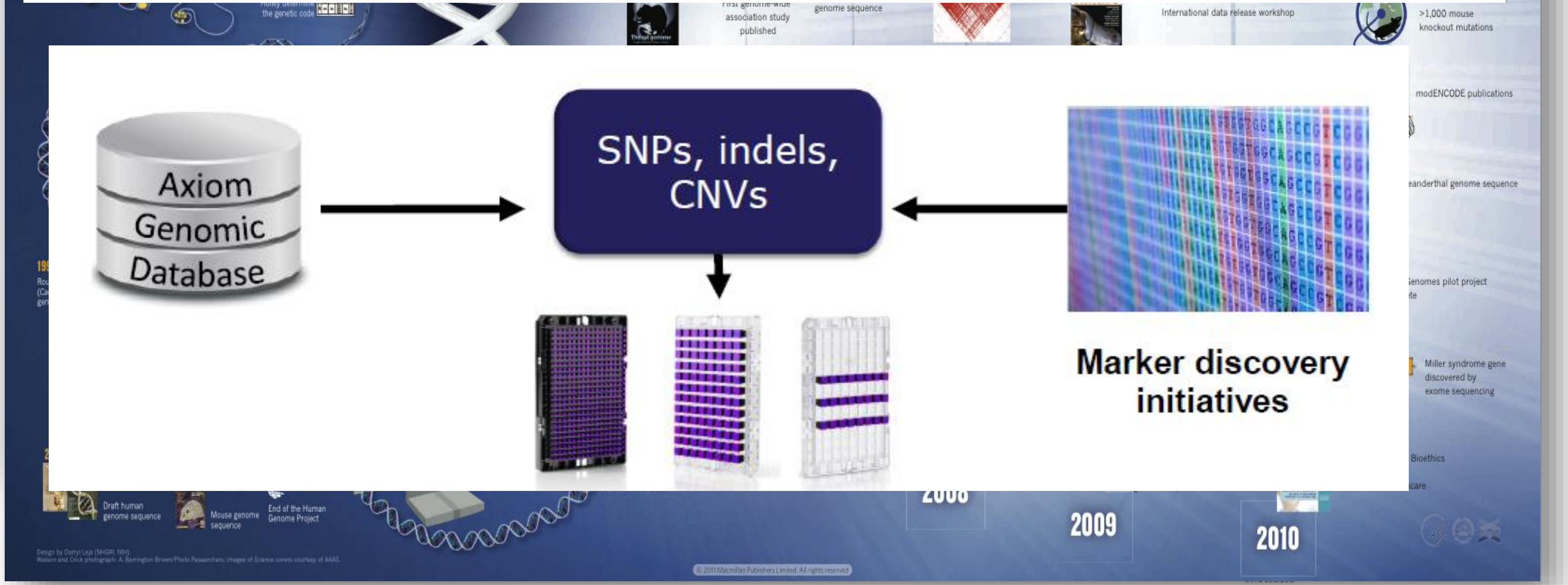


Global Lipid Genetic Consortium [10] 12 SNP LDL-C Gene Score, showing the LDL-C-raising allele and the published raising effect (in mmol/l).

CHR	SNP	Gene	Minor[a]	Common[a]	GLGC weight
1	rs2479409	*PCSK9*	**G**	A	0.052
1	**rs629301**	***CELSR2***	G	**T**	0.15
2	**rs1367117**	***APOB***	**A**	G	0.10
2	**rs4299376**	***ABCG8***	**G**	T	0.071
6	rs1564348	*SLC22A1*	C	**T**	0.014
6	rs1800562	*HFE*	A	**G**	0.057
6	rs3757354	*MYLIP*	T	**C**	0.037
11	rs11220462	*ST3GAL4*	**A**	G	0.050
14	rs8017377	*KIAA1305*	**A**	G	0.029
19	**rs6511720**	***LDL-R***	T	**G**	0.18
19	**rs429358**	***APOE***	C	T	
19	**rs7412**	***APOE***	T	C	
		ε2ε2			−0.9
		ε2ε3			−0.4
		ε2ε4			−0.2
		ε3ε3			0
		ε3ε4			0.1
		ε4ε4			0.2

GLGC weights from Ref. [10] and *APOE* weights were based on haplotypic effects taken from [42].

[a] Risk alleles (LDL-C-raising) are indicated in bold. rs numbers and gene symbols in bold indicate the 6-SNPs used in [15].



Salut/ Germans Trias i Pujol Hospital

ORIGINAL RESEARCH

JACC Adv. 2022;1(3):100068.

GENETICS, OMICS, AND TISSUE REGENERATION

Clinical Implementation of Combined Monogenic and Polygenic Risk Disclosure for Coronary Artery Disease

Dimitri J. Maamari, MD,[a,b,c,*] Deanna G. Brockman, MS, CGC,[a,b,*] Krishna Aragam, MD, MS,[b,d,e] Renée C. Pelletier, MS, CGC,[a,b] Emma Folkerts, BS,[a] Cynthia L. Neben, PhD,[f] Sydney Okumura, BS,[f] Leland E. Hull, MD, MPH,[e,g] Anthony A. Philippakis, MD, PhD,[b] Pradeep Natarajan, MD, MMSC,[a,b,d,e,h] Patrick T. Ellinor, MD, PhD,[b,d,e,h] Kenney Ng, PhD,[i] Alicia Y. Zhou, PhD,[f] Amit V. Khera, MD, MSc,[a,b,d,e,h,j,†] Akl C. Fahed, MD, MPH[a,b,d,e,h,†]

Initial visit, 60 participants enrolled at a Preventive Genomics Clinic

Combined genetic risk assessment for CAD:
- Monogenic: Sequencing of *LDLR*, *APOB* and *PCSK9*
- Polygenic: Score consisting of 6.6 million common variants

Baseline survey prior to return of results

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SOCIETAT CATALANA D'ENDOCRINOLOGIA I NUTRICIÓ

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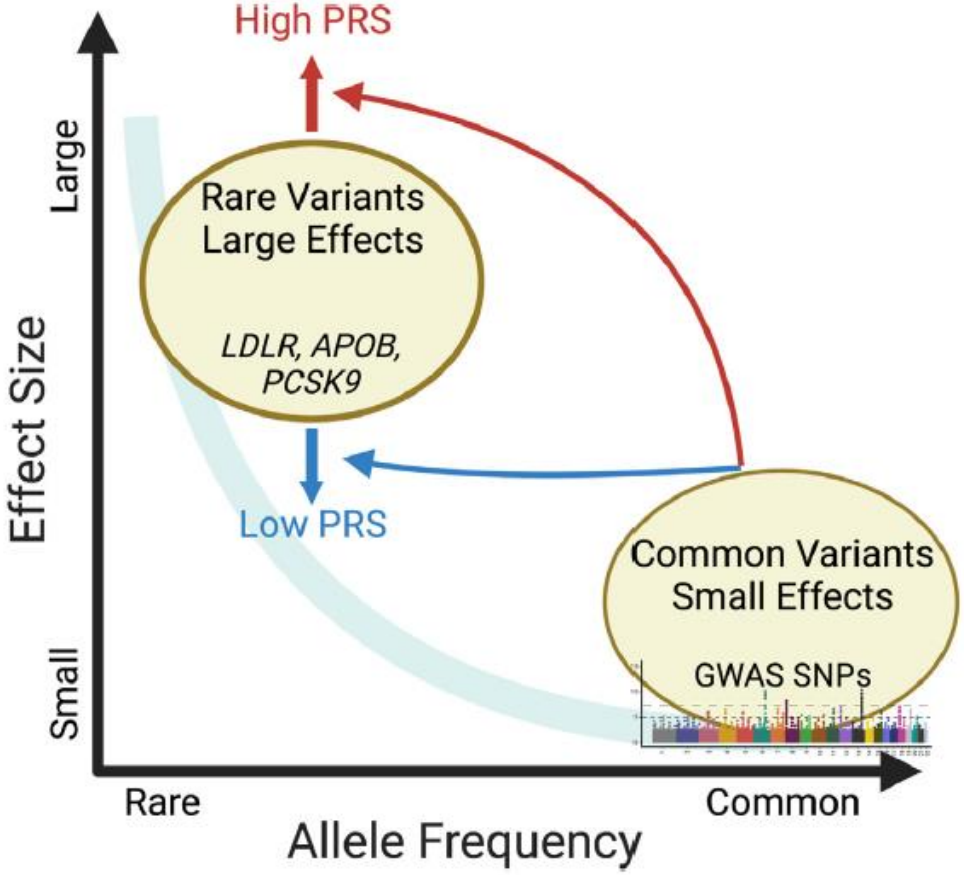
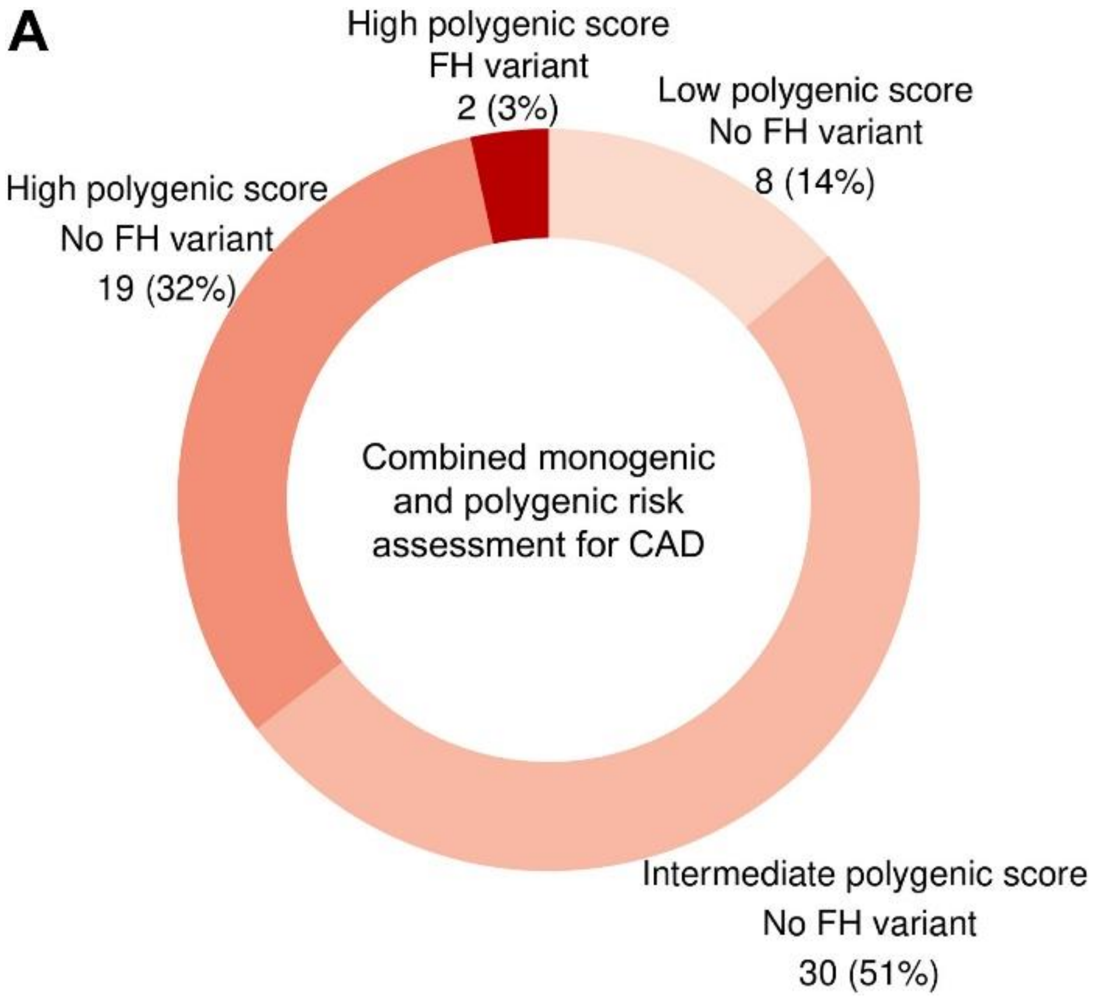
JACC: ADVANCES, VOL. 2, NO. 9, 2023
NOVEMBER 2023:100663

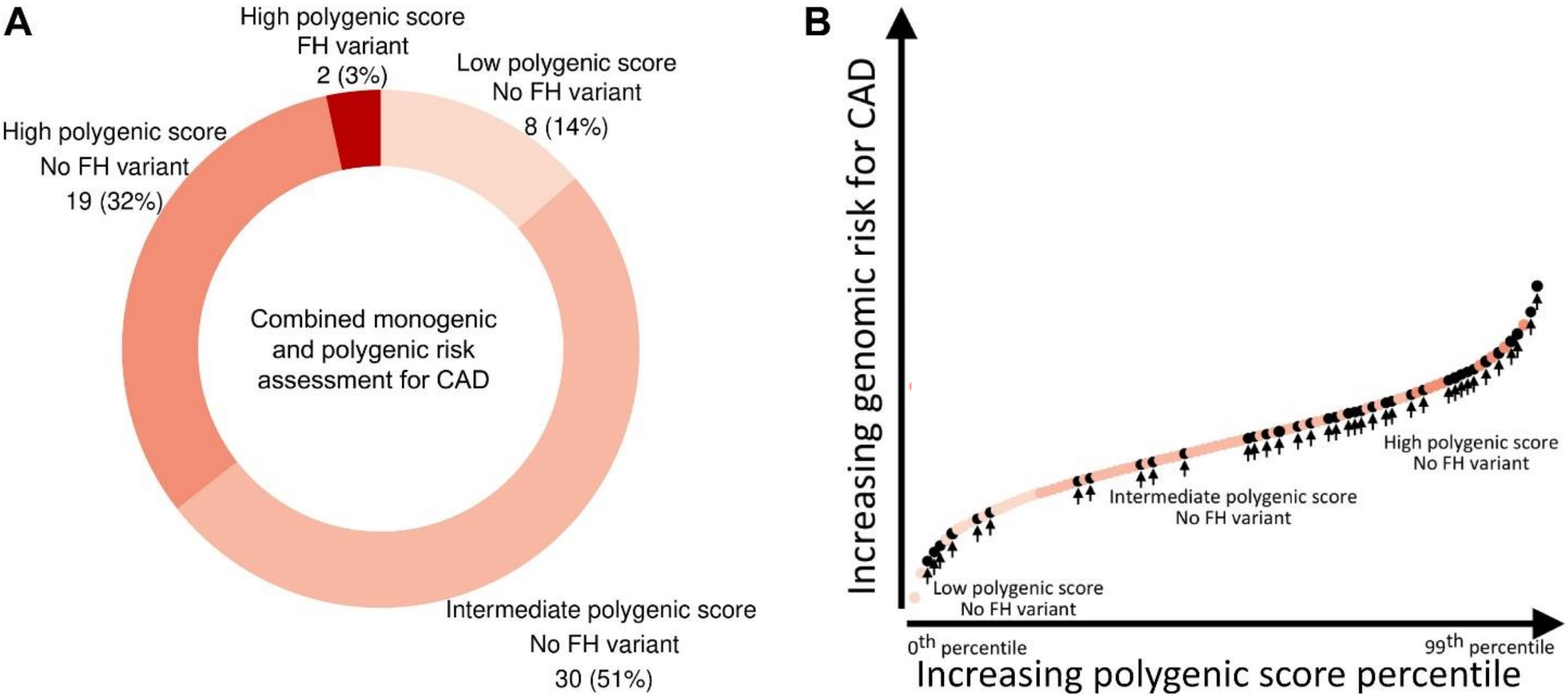
Another Use for Polygenic Risk Scores

Improving Risk Prediction for Heterozygous Familial Hypercholesterolemia*

Brian T. Palmisano, MD, PhD,[a,b] Joshua W. Knowles, MD, PhD[a,b,c,d]




A
High polygenic score
FH variant
2 (3%)
Low polygenic score
No FH variant
8 (14%)
High polygenic score
No FH variant
19 (32%)
Combined monogenic
and polygenic risk
assessment for CAD
Intermediate polygenic score
No FH variant
30 (51%)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High polygenic score
No FH variant
19 (32%)
Combined monogenic and polygenic risk assessment for CAD
Intermediate polygenic score
No FH variant
30 (51%)
B
Increasing genomic risk for CAD
High polygenic score
No FH variant
Intermediate polygenic score
No FH variant
Low polygenic score
No FH variant
0th percentile
99th percentile
Increasing polygenic score percentile

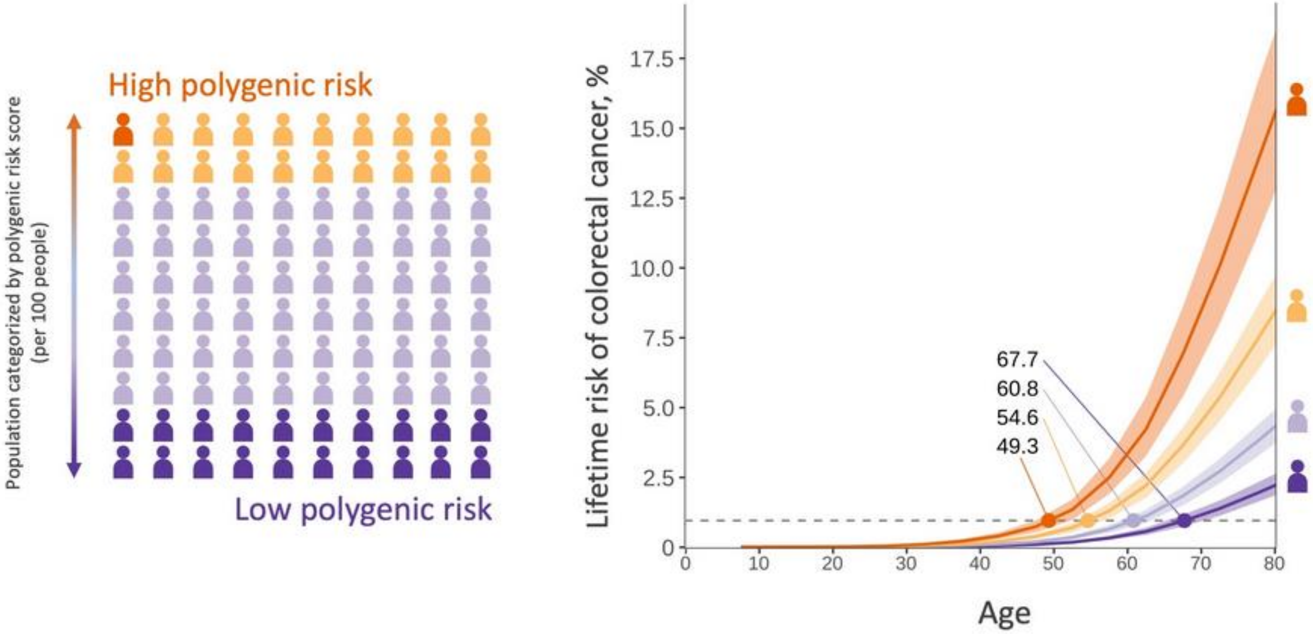
Received: 22 March 2023 | Revised: 11 May 2023 | Accepted: 29 May 2023
DOI: 10.1111/cge.14387

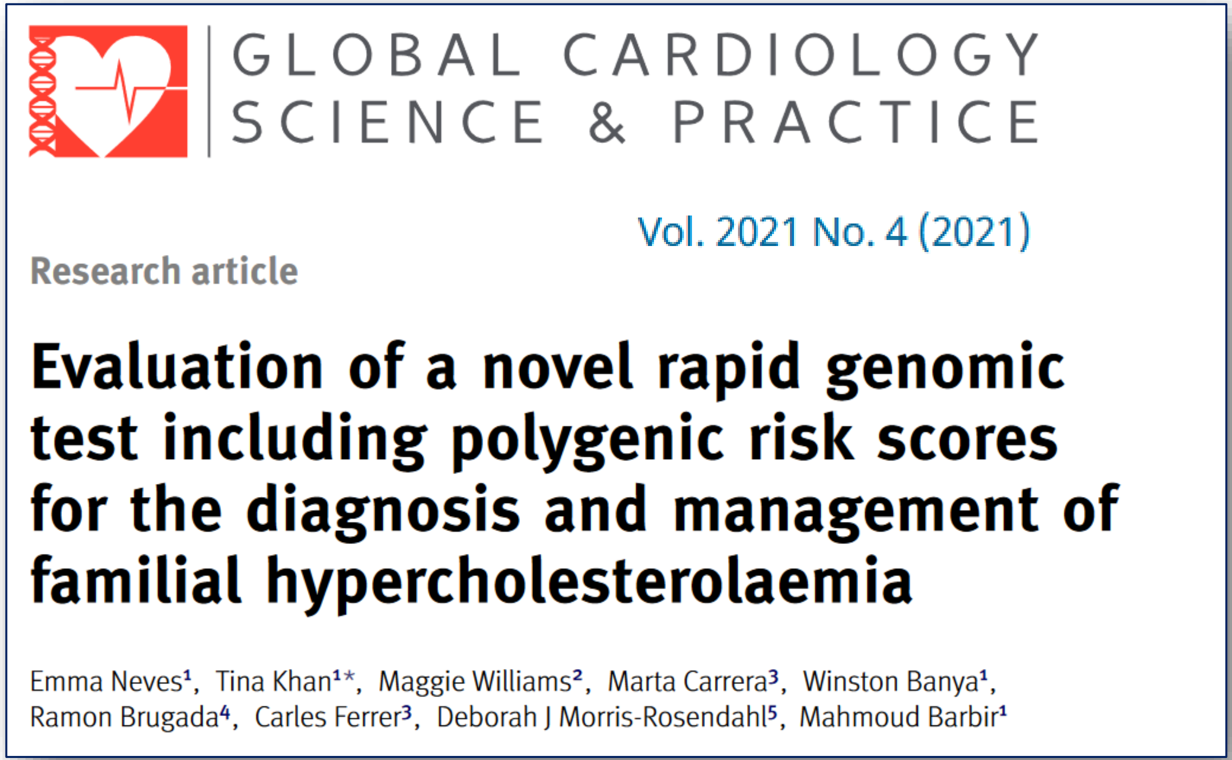
ORIGINAL ARTICLE

CLINICAL GENETICS WILEY

Filling the gap: Genetic risk assessment in hypercholesterolemia using LDL-C and LPA genetic scores

Gunda Schwaninger[1] | Lukas Forer[2] | Christoph Ebenbichler[3] | Hans Dieplinger[2] | Florian Kronenberg[2] | Johannes Zschocke[1] | Martina Witsch-Baumgartner[1]



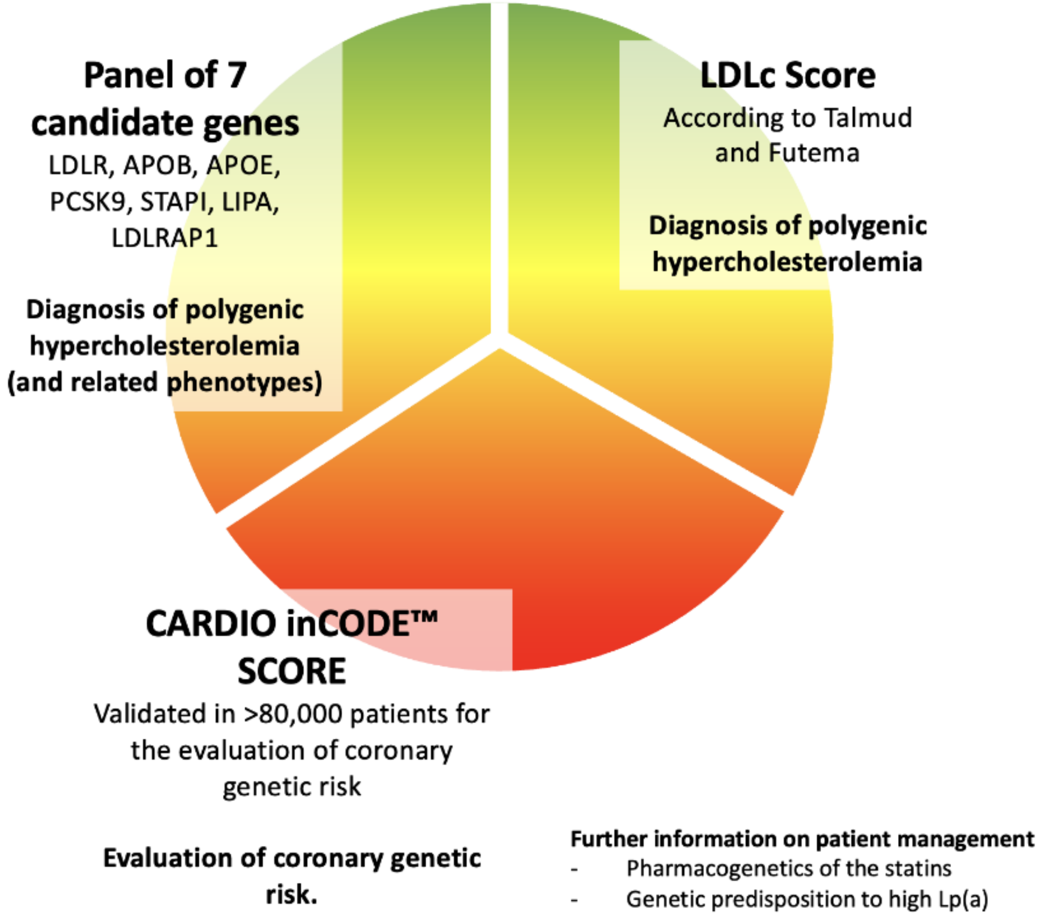

GLOBAL CARDIOLOGY SCIENCE & PRACTICE

Vol. 2021 No. 4 (2021)

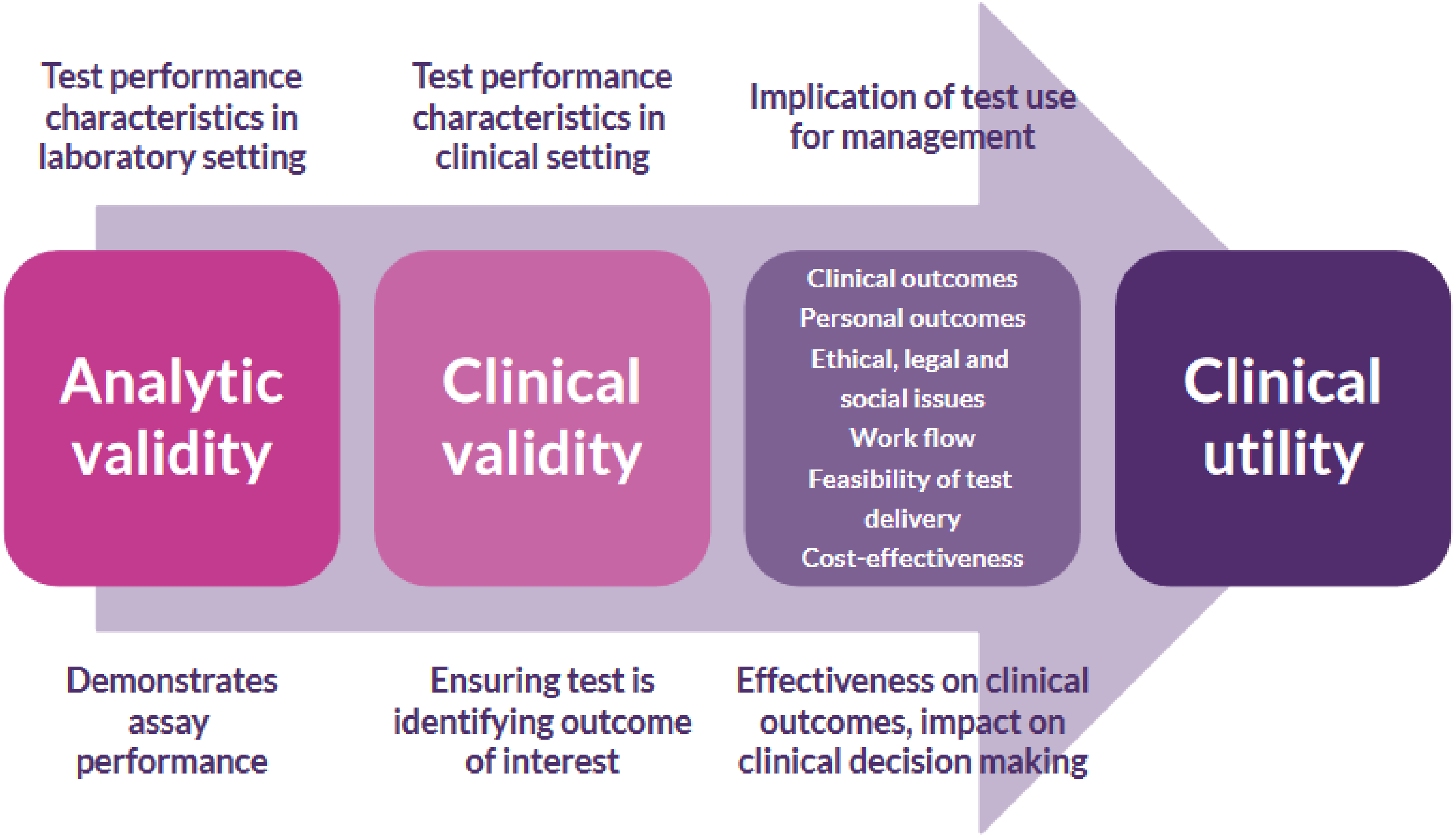
Research article

Evaluation of a novel rapid genomic test including polygenic risk scores for the diagnosis and management of familial hypercholesterolaemia

Emma Neves[1], Tina Khan[1*], Maggie Williams[2], Marta Carrera[3], Winston Banya[1], Ramon Brugada[4], Carles Ferrer[3], Deborah J Morris-Rosendahl[5], Mahmoud Barbir[1]



Monogenic diagnosis with polygenic risk stratification.


Test performance characteristics in laboratory setting
Test performance characteristics in clinical setting
Implication of test use for management
Analytic validity
Clinical validity
Clinical outcomes
Personal outcomes
Ethical, legal and social issues
Work flow
Feasibility of test delivery
Cost-effectiveness
Clinical utility
Demonstrates assay performance
Ensuring test is identifying outcome of interest
Effectiveness on clinical outcomes, impact on clinical decision making

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Catálogo de Pruebas Genéticas y Genómicas

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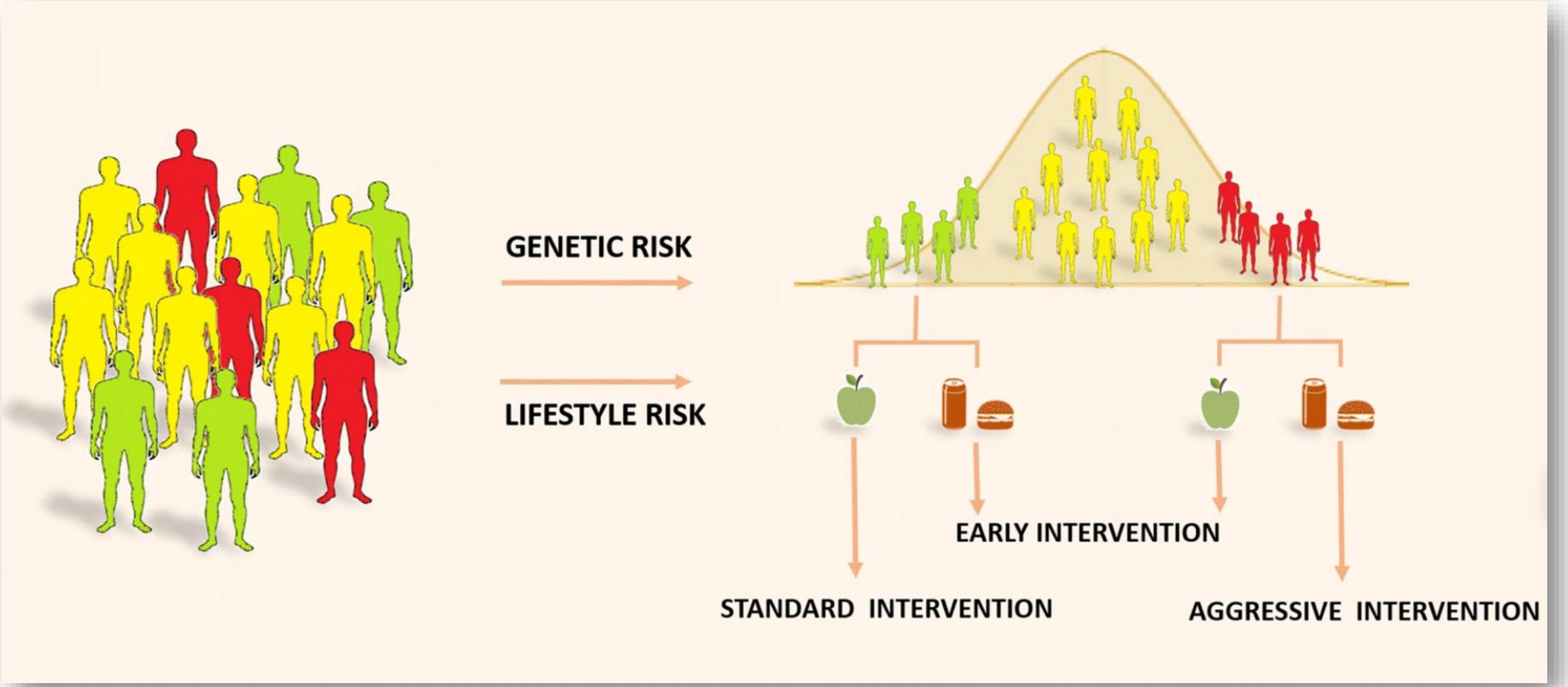
Catálogo Común de Pruebas Genéticas y Genómicas del SNS

Las pruebas genéticas y genómicas constituyen un elemento esencial para el diagnóstico y pronóstico de enfermedades de alto impacto sanitario como son las enfermedades raras y oncológicas, y la selección y el seguimiento de tratamientos óptimos.
El acceso a este catálogo como parte de la cartera común de servicios debe garantizarse a todos los usuarios del SNS.

Mas Información


GENETIC RISK
LIFESTYLE RISK
EARLY INTERVENTION
STANDARD INTERVENTION
AGGRESSIVE INTERVENTION

Salut/ Germans Trias i Pujol Hospital

Societat Catalana d'Endocrinologia i Nutrició

L'Acadèmia

Gracias

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