Penn Medicine

ACC India 2023 Cardiovascular Symposium

Premature Coronary Artery Disease: *Role of Genetic Testing and Polygenic Risk Scores*

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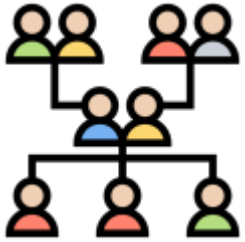
Section for Advanced Heart Failure, Transplantation, and Mechanical Support

January 21, 2023

29-year-old man presents to clinic for evaluation



Mother with high cholesterol and MI in her 50s
Maternal grandfather died from heart disease at age 54

No goiter, vascular bruits, xanthomata / xanthelasma, corneal arcus

Exercises 4 days per week, does not smoke
BP 112/68. HbA1c 5.0%
LDL-C = 227 mg/dL

Learning Objectives

What are the genetic contributions to premature coronary artery disease?

How can we diagnose these genetic risk factors?

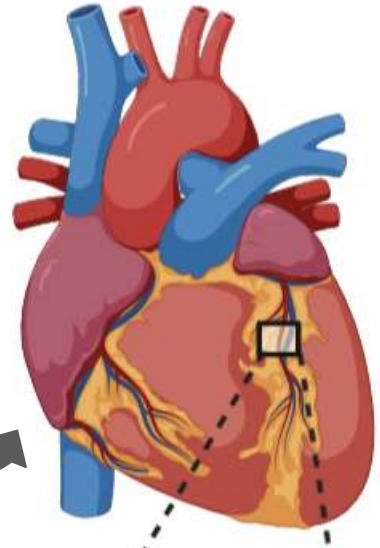
What are the challenges to deploying these tools in routine clinical practice?

How does genetics predispose individuals to coronary artery disease?

Monogenic disease

Single variant → large effect

Disrupts specific pathway



Polygenic disease

Many variants → each with small effect

Affects many pathways

Familial hypercholesterolemia (FH) is a genetic condition that results in premature CAD due to lifelong exposure to elevated LDL-C

Heterozygous FH ~1:220

Homozygous FH ~1:200,000-300,000

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♂ **50% by age 50**

♀ **30% by age 60**

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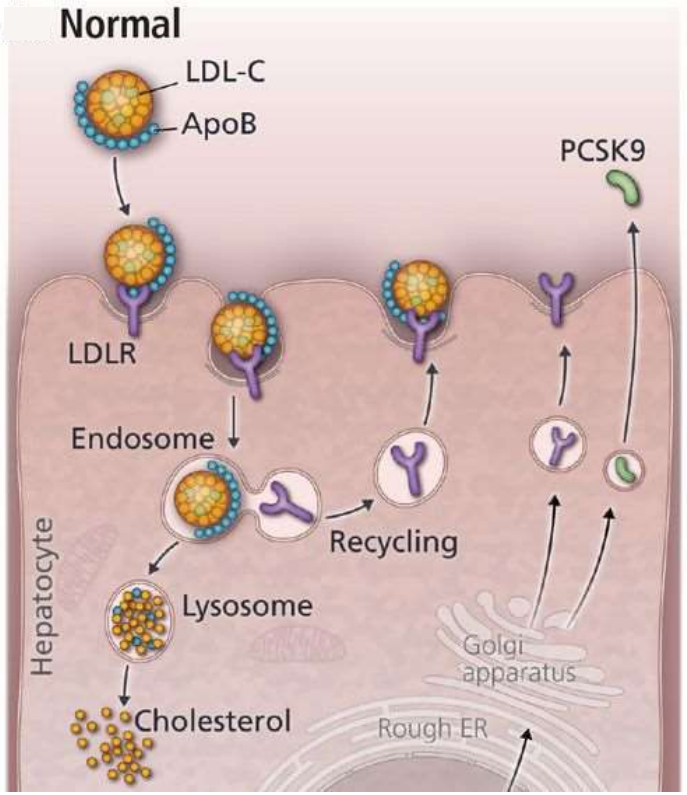
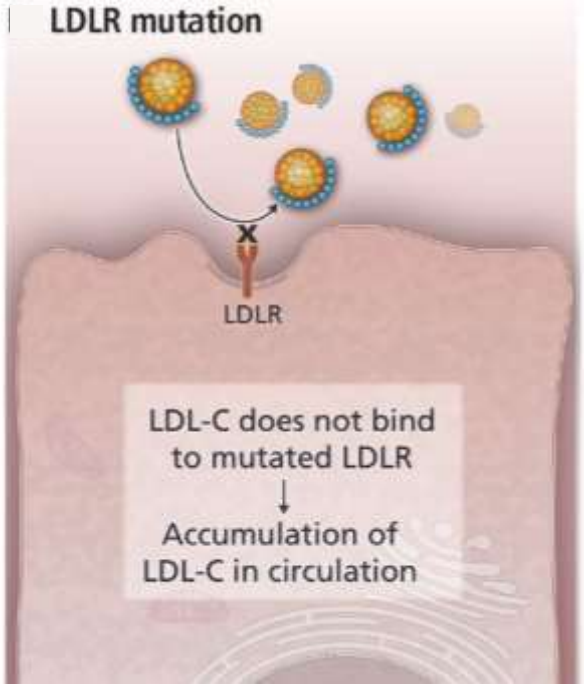
♂ 50% by age 50

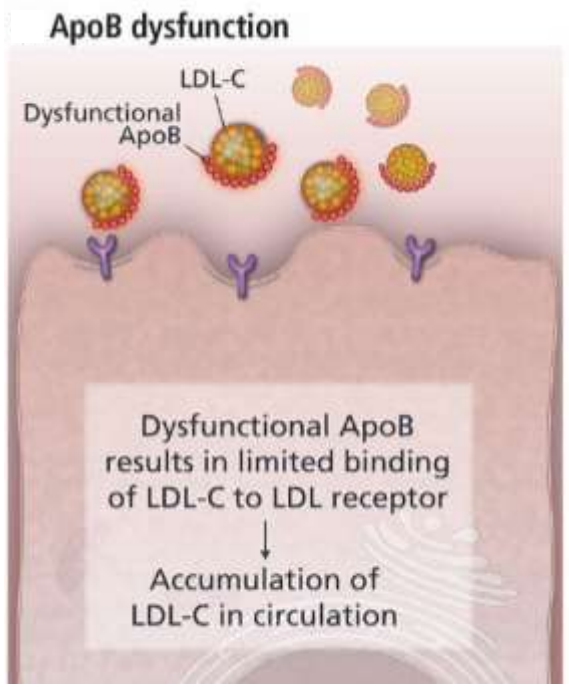
♀ 30% by age 60





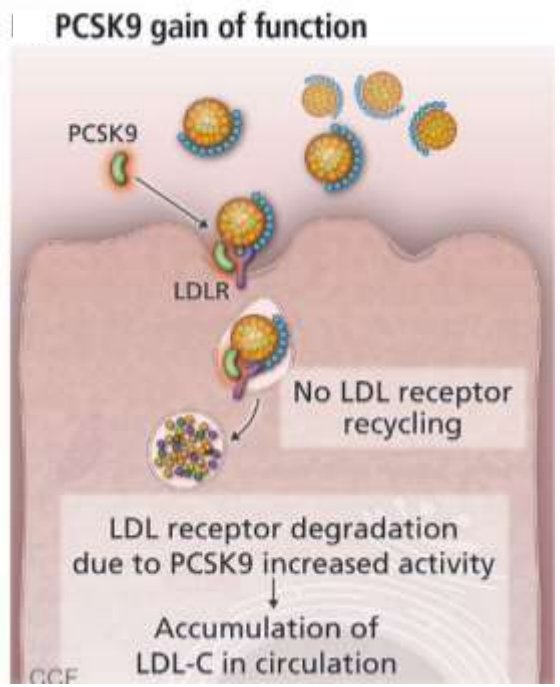
~80-90%

Autosomal co-dominant



~5-10%

Autosomal co-dominant



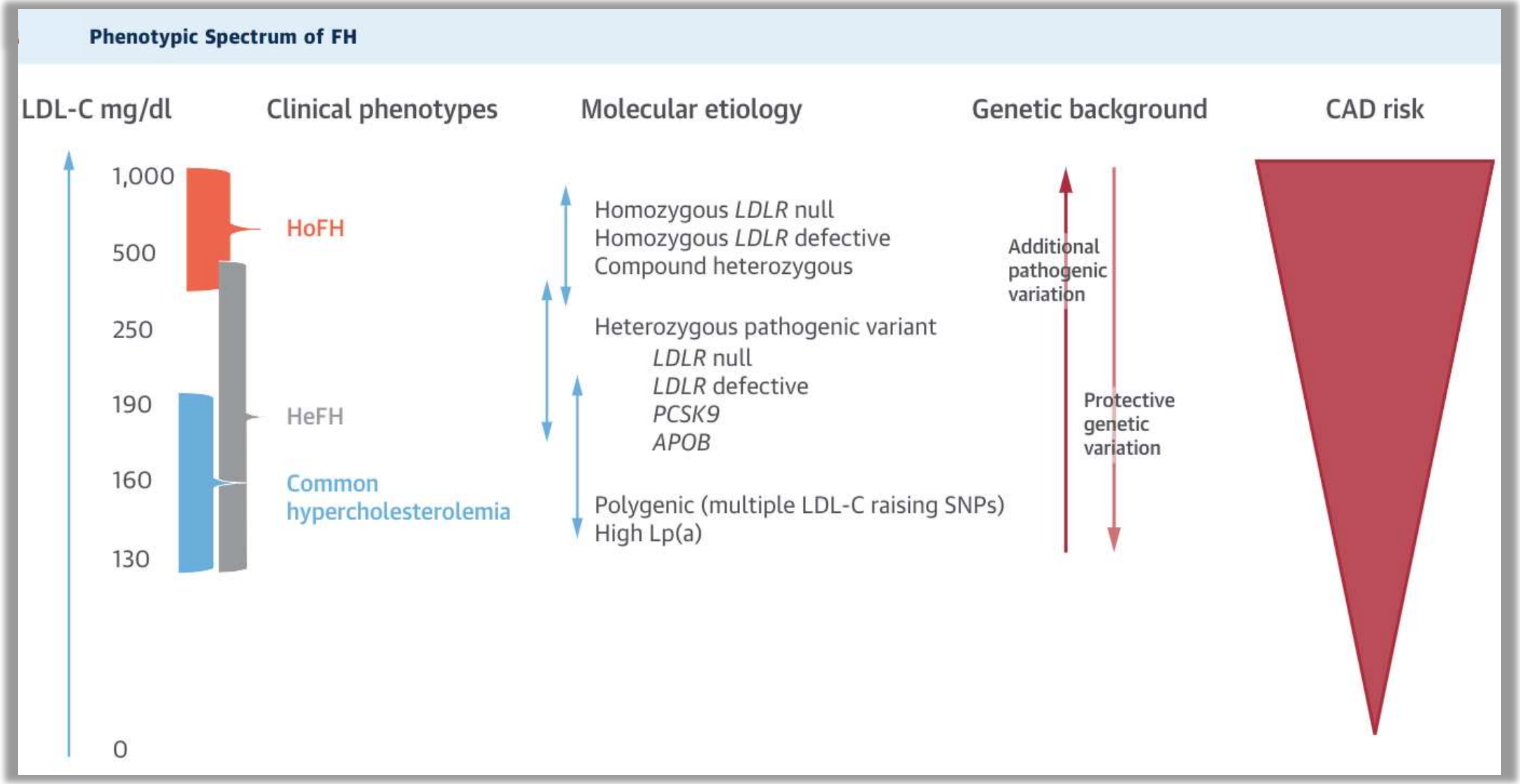
<1%

Autosomal co-dominant

Sturm, A et al. JACC. 2018; 72(6):662-680

Shah NP, et al. Cleve Clin J Med. 2020;87(2):109-120

FH encompasses a spectrum of clinical phenotypes, based in part on the various pathogenic variants



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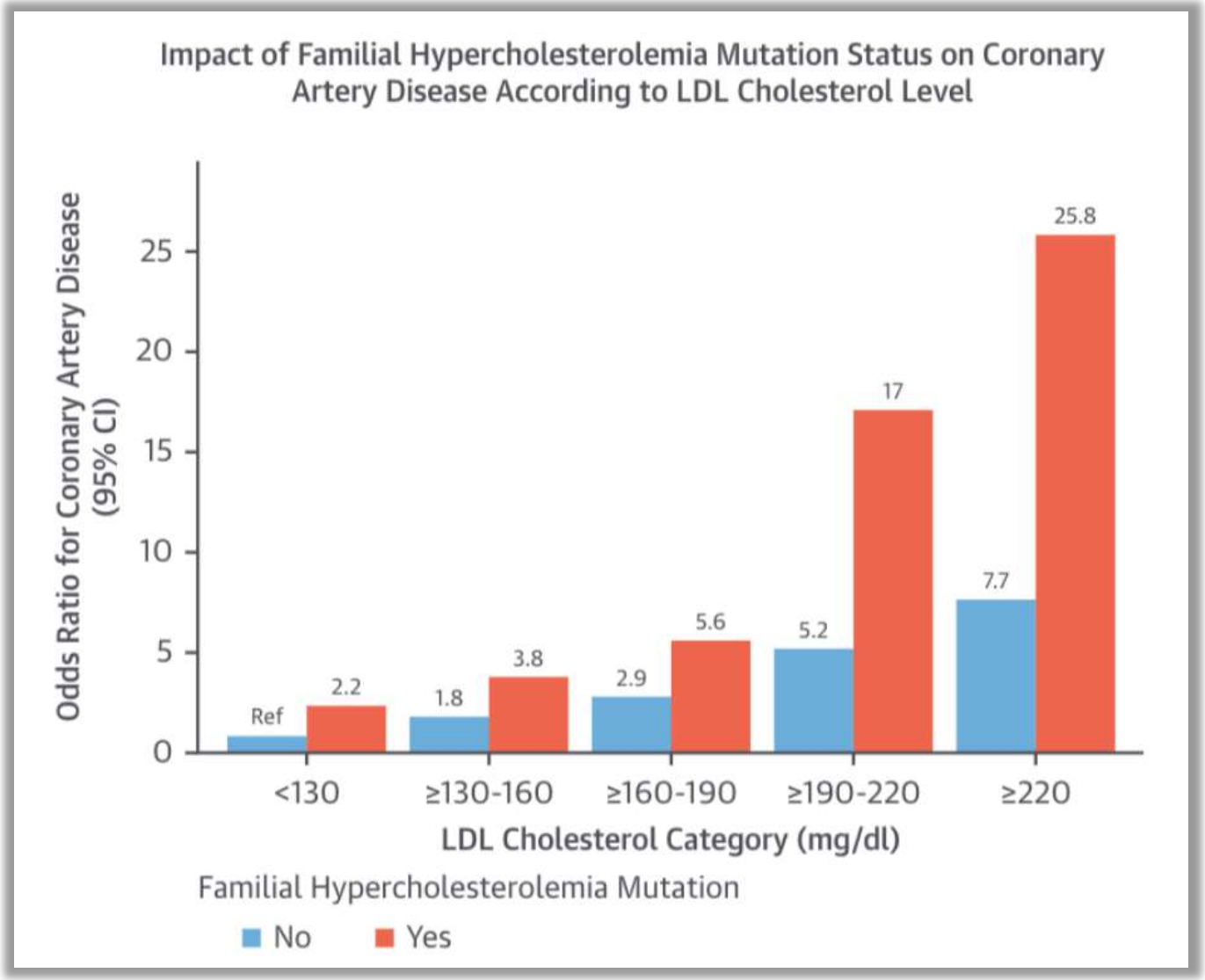
CAD risk is higher in FH pathogenic variant carriers compared to noncarriers at any LDL-C value



FH pathogenic variant increases CAD risk ~3-4x at same LDL-C level

Sturm, A et al. JACC. 2018; 72(6):662-680

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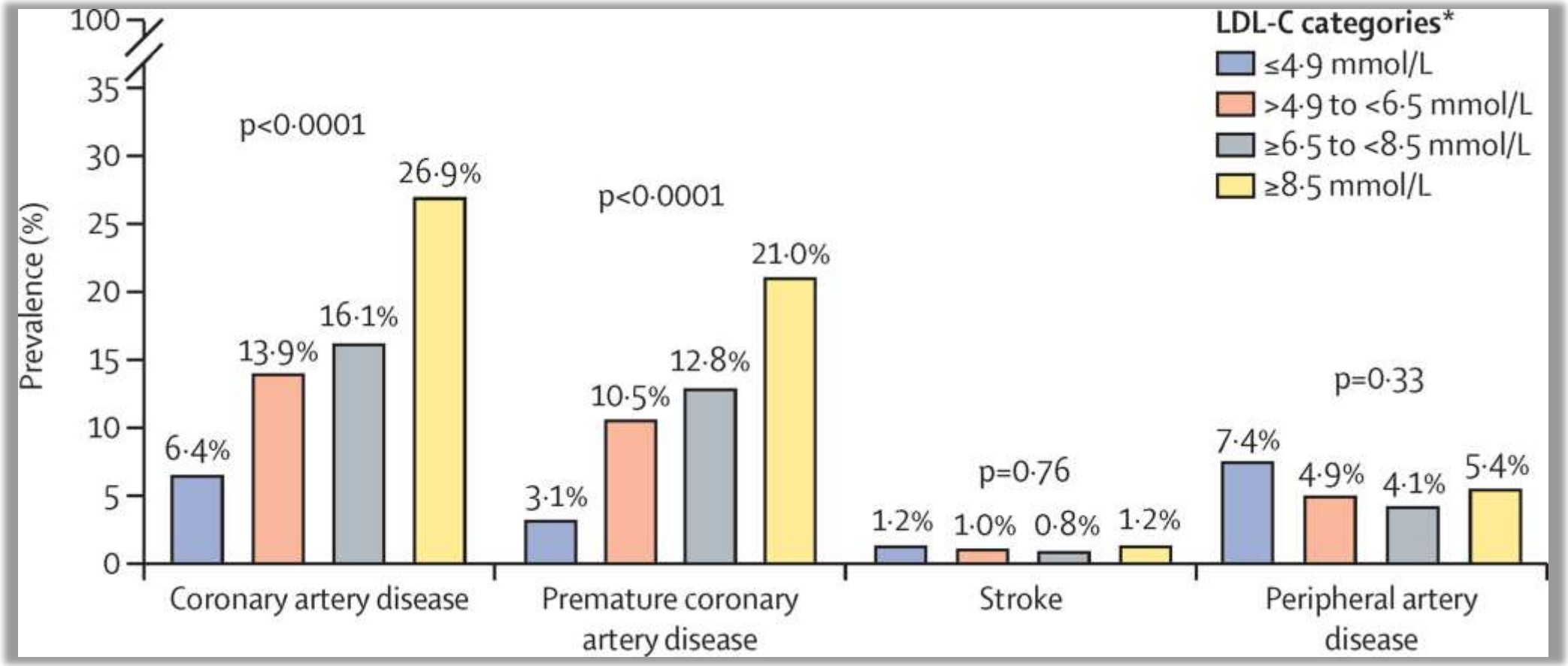
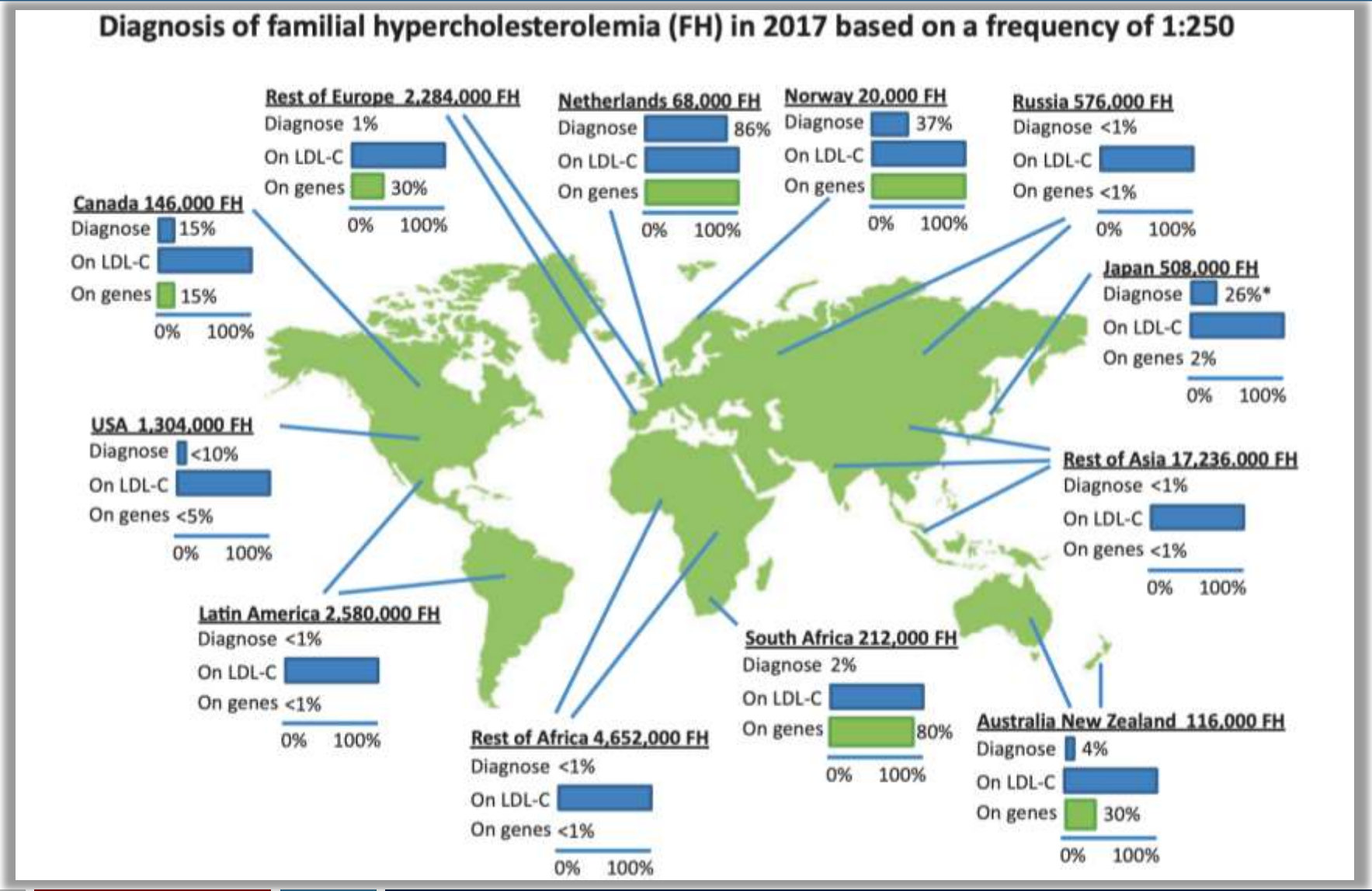
Global registry of 61,612 individuals with FH



Progressively increased CAD prevalence with increasing concentrations of untreated LDL-C

>90% of the ~30 million individuals with FH worldwide are undiagnosed



Nordestgaard BG and Benn M. Eur Heart J. 2017; 38:1580-1583

FH is clinically diagnosed by a weighted combination of physical findings, personal / family history of hypercholesterolemia, early-onset ASCVD, LDL-C levels, and genetics

Criteria	MEDPED	DUTCH	SIMON BROOME	NLA*	AHA
Family history of premature CAD		+	+	+	+
Family history of tendon xanthomas		+	+		
Family history of hypercholesterolemia	+	+	+	+	
Patient premature CAD		+		+	
Patient premature PVD		+			
Tendon xanthomas		+	+	+	
Corneal arcus		+		+	
Elevated LDL-C	+	+	+	+	+
Genetic mutation		+	+	+	+

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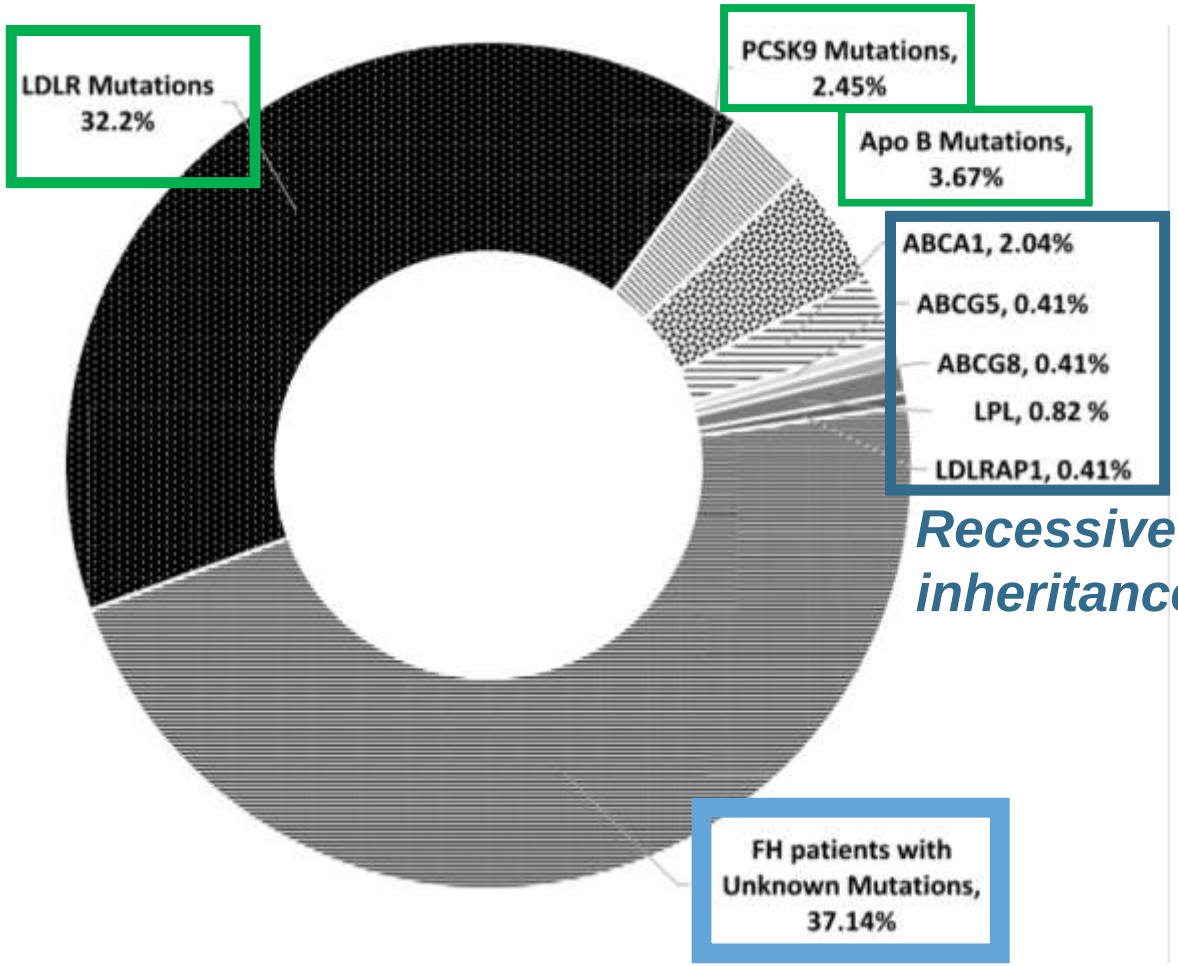
Corneal arcus		+		+	
Elevated LDL-C	+	+	+	+	+
Genetic mutation		+	+	+	+

Scoring systems have been developed in Western cohorts

In India, there remain many opportunities to learn more regarding the genetics and overall prevalence of individuals with FH



Recessive inheritance

Reddy, LL et al. Indian Heart Journ. 2022; 74(1):1-6

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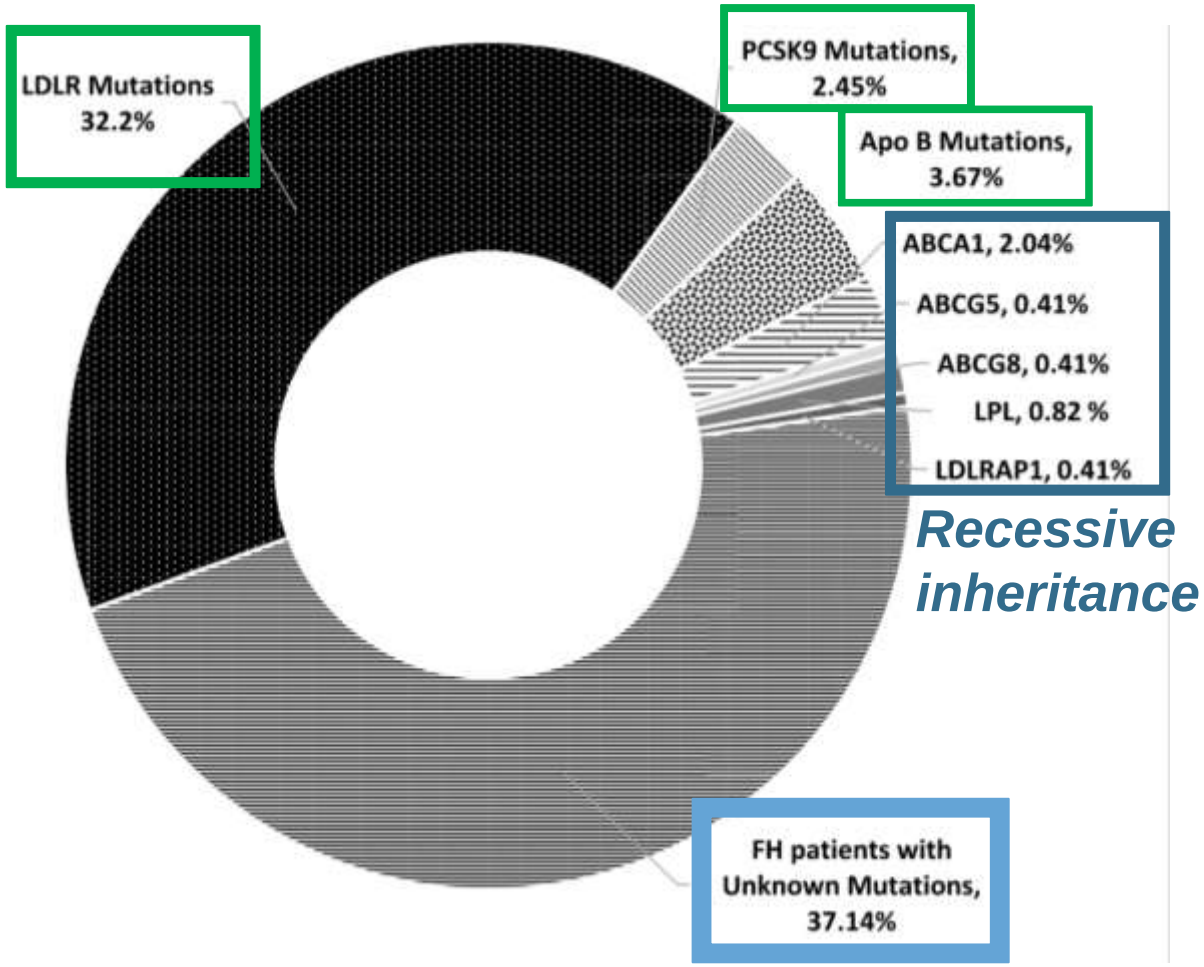


Recessive inheritance

635 consecutive patients with ACS or angina

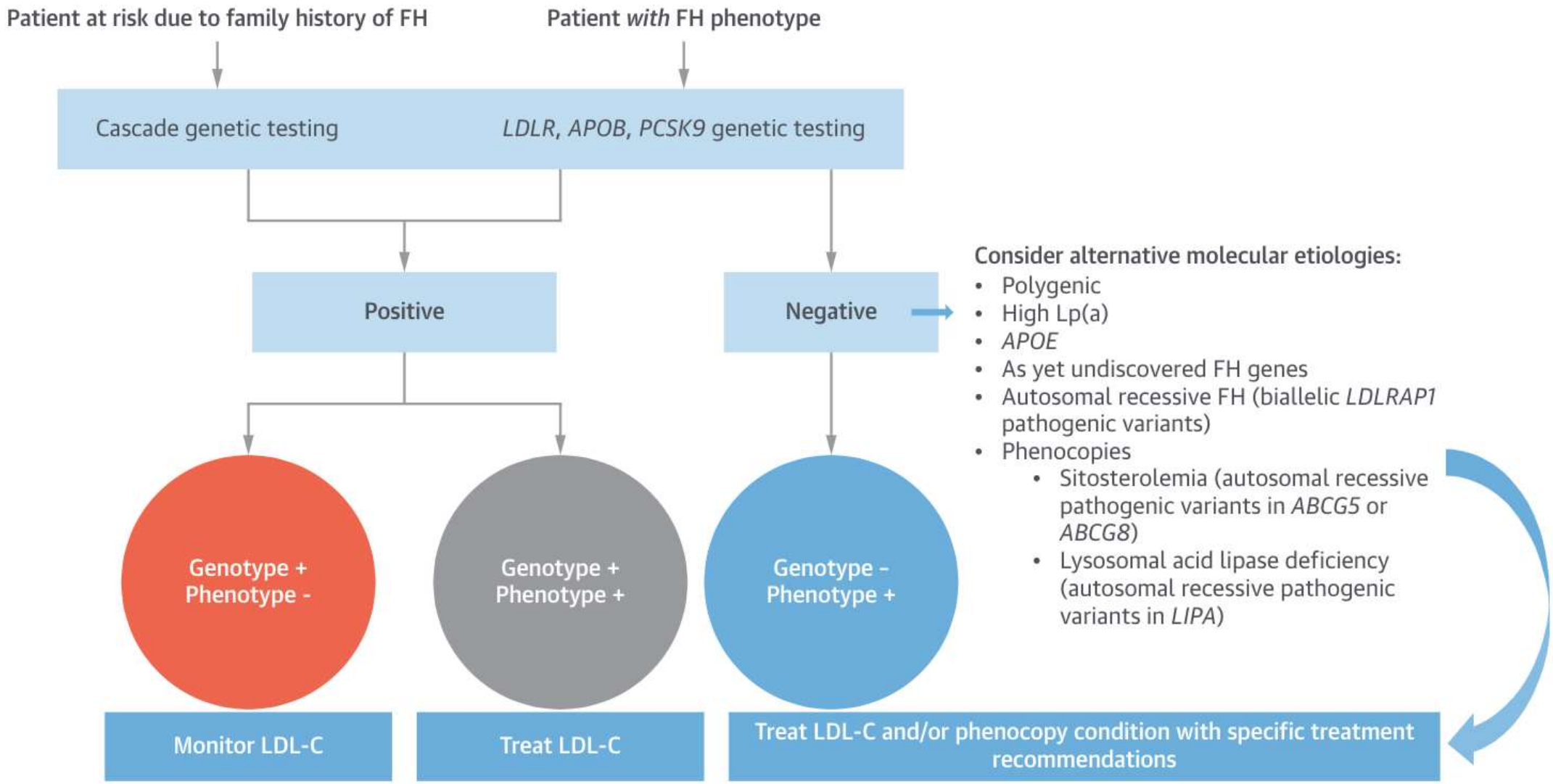
4% Definite

11% Probable

37% Possible

Using DLCN criteria

To best identify and treat patients with FH, both genotype+ and phenotype+ definitions should be used



Sturm, A et al. JACC. 2018; 72(6):662-680

Genetic testing for FH should be offered to individuals of any age, including:
Children LDL-C ≥ 160 mg/dl or Adults LDL-C ≥ 190 mg/dl • without secondary cause of hypercholesterolemia *and* • with ≥ 1 first-degree relative affected or with premature CAD or where family history unavailable
Children LDL-C ≥ 190 mg/dl or Adults LDL-C ≥ 250 mg/dl • without secondary cause of hypercholesterolemia, even in absence of a positive family history

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Genetic testing for FH may be considered in individuals including:
Children LDL-C ≥ 160 mg/dl without a secondary cause and with ≥ 1 parent with LDL-C ≥ 190 mg/dl or a family history of hypercholesterolemia and premature CAD
Adults with no pre-treatment LDL-C but with a personal history of premature CAD and family history of both hypercholesterolemia and premature CAD
Adults LDL-C ≥ 160 mg/dl without a secondary cause in the setting of a family history of hypercholesterolemia and either a personal history or a family history of premature CAD

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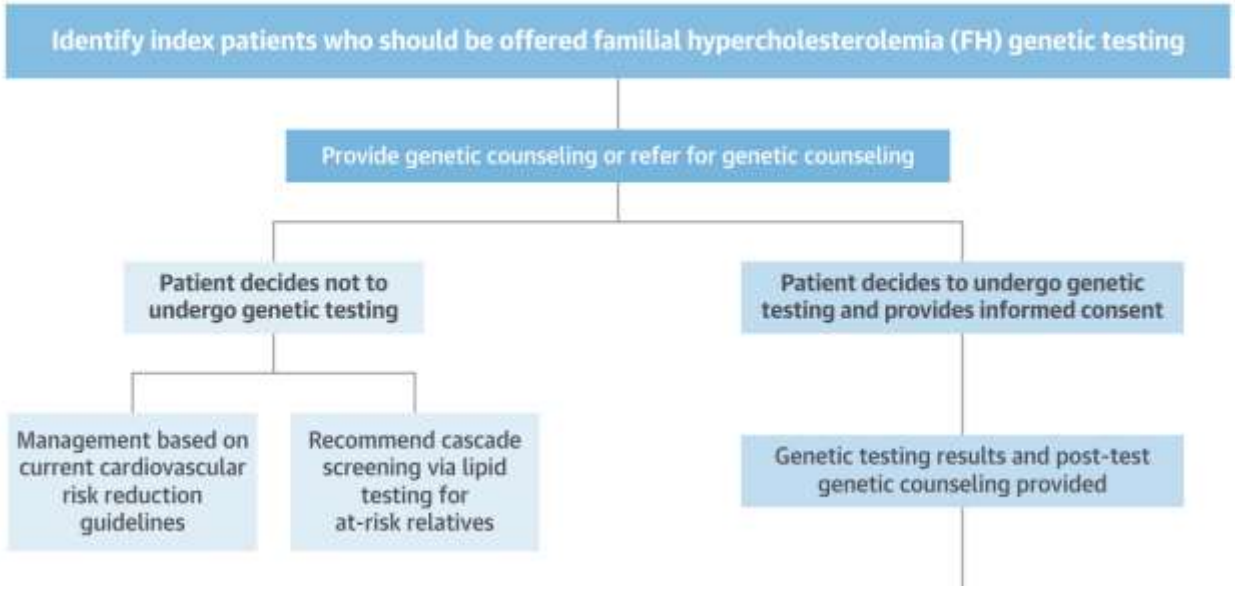

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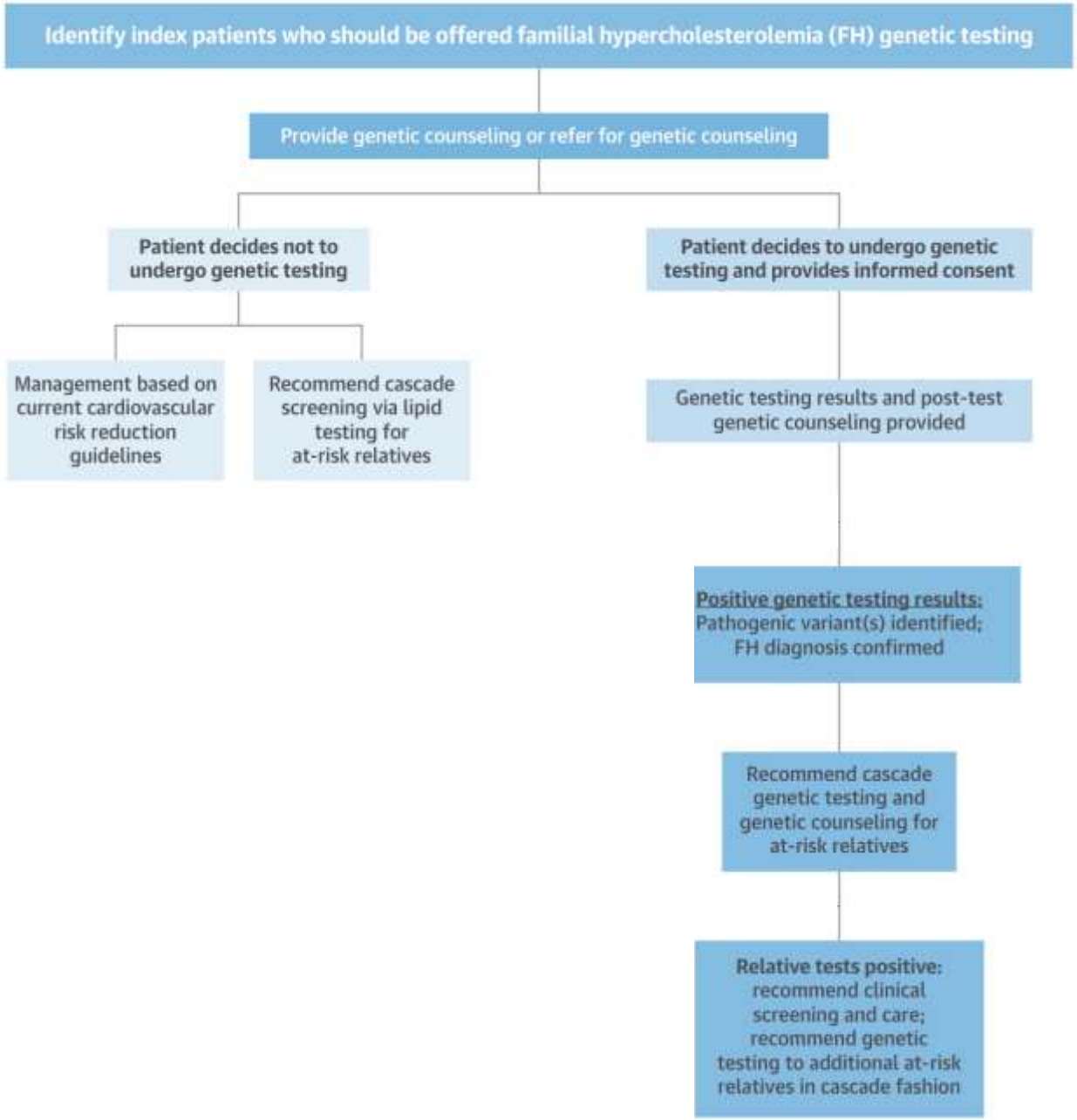

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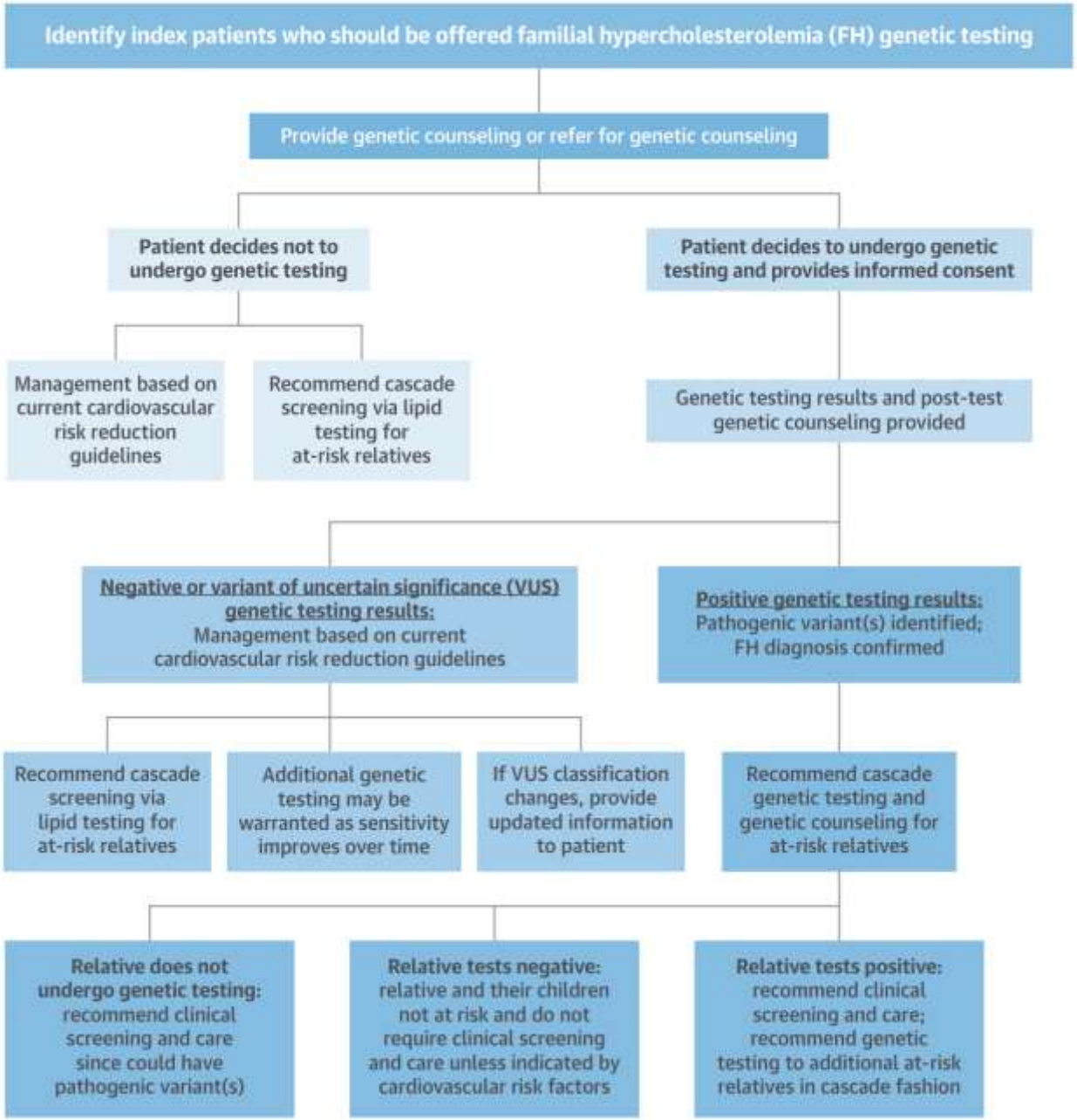

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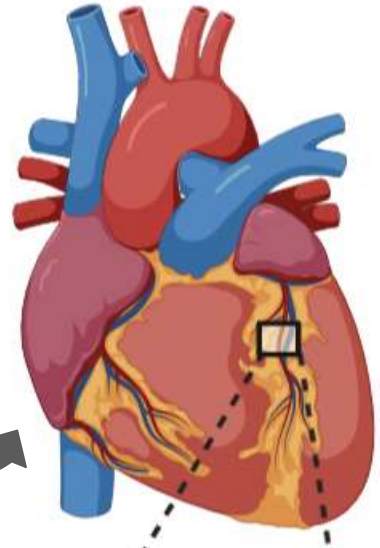
How does genetics predispose individuals to coronary artery disease?

Monogenic disease

Single variant → large effect

Disrupts specific pathway



Polygenic disease

Many variants → each with small effect

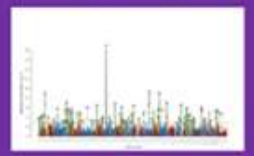
Affects many pathways

Polygenic risk scores (PRS) are the weighted sum of the risk conferred by multiple disease-associated single nucleotide variants across the genome

PRS SUBSTRATE

Discovery dataset

GWAS



GWAS summary statistics

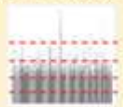
SNP	Risk allele	β
rs1234	C	0.456
rs1345	G	0.215
...	T	0.345
....	....	0.132
.....	....	....

PRS CALCULATION

LD adjustment

i.e. clumping

P-value thresholding



i.e. multiple P thresholds

Clumping & Thresholding scores

Beta shrinkage

i.e. LDpred, lassosum

Genome-wide scores

PRS TRAINING

Training dataset

Generate multiple PRS

ID	Age	PRS
101	45	0.41
102	52	3.23
103	47	1.45

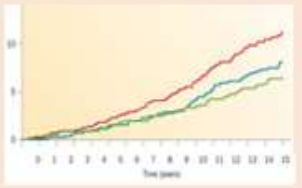
Perform association testing

Identify "best" score parameters

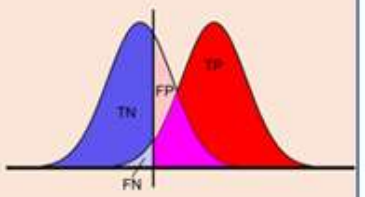
PRS VALIDATION

Validation dataset

Test "best" score



Report performance metrics

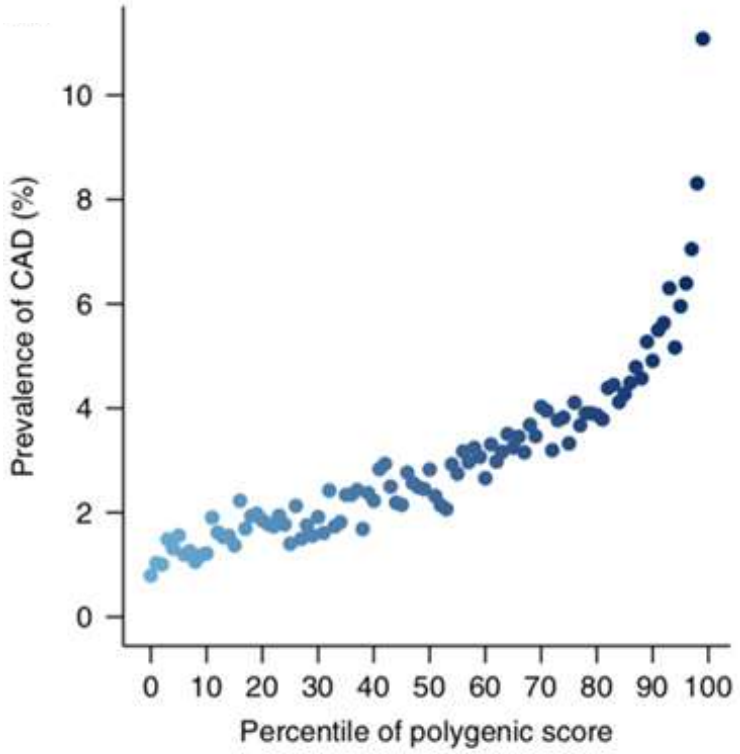


i.e. AUC, p-value, HR

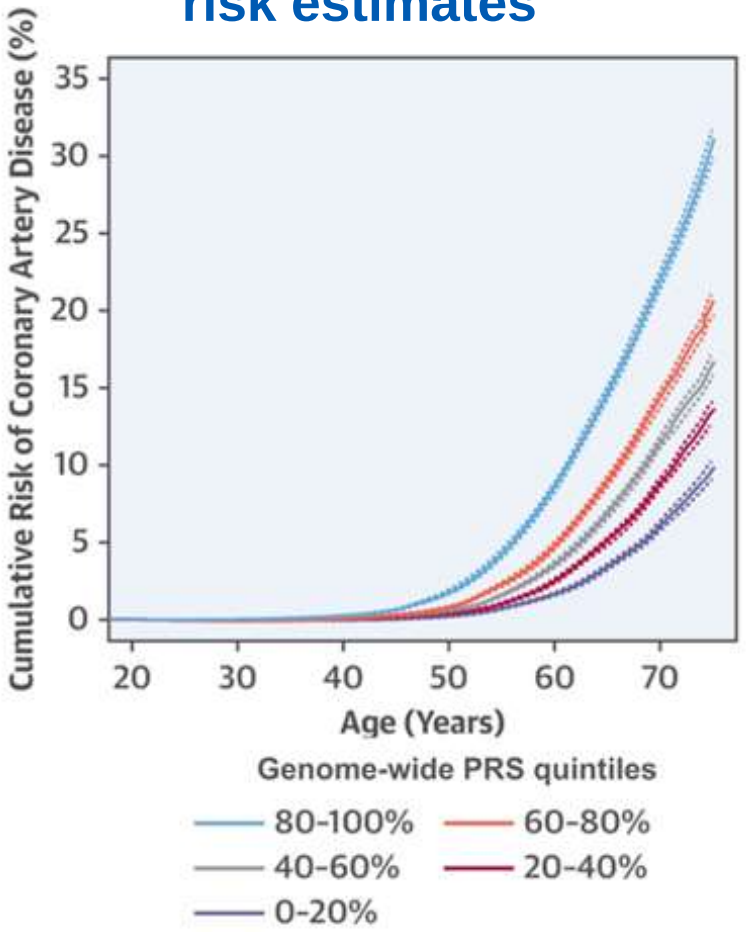
Aragram KG and Natarajan P. Circ Res. 2020;126(9):1159-1177.

Genome-wide PRS have the potential to enhance CAD risk prediction

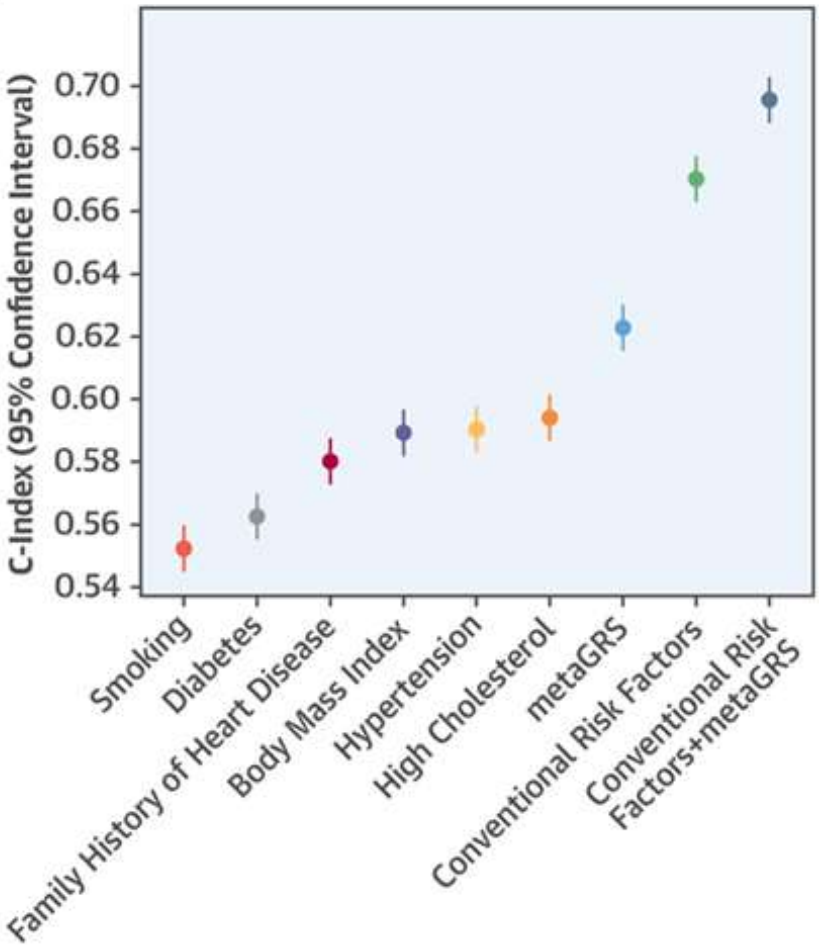
Identify inherited predisposition to CAD



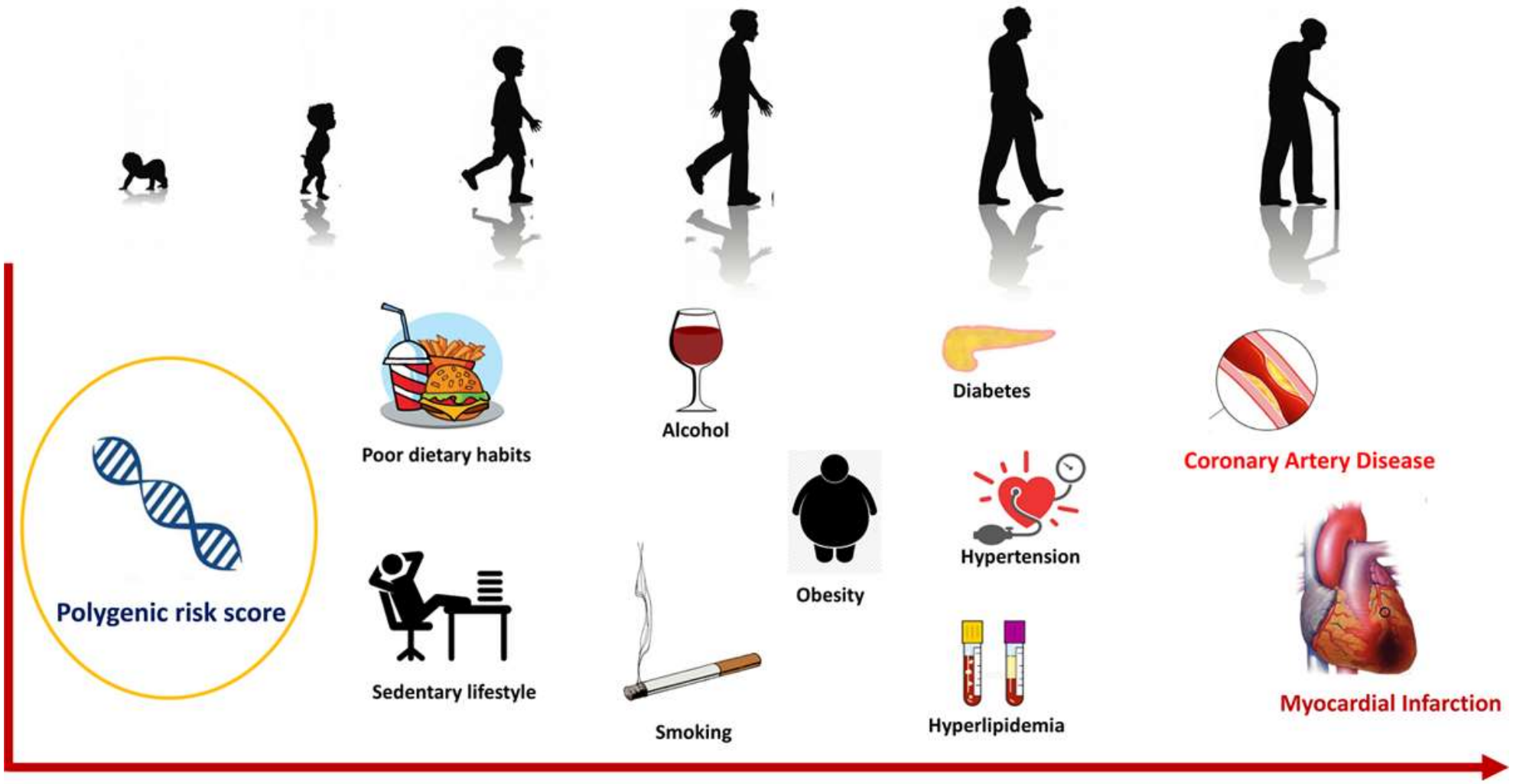
Provide lifetime CAD risk estimates



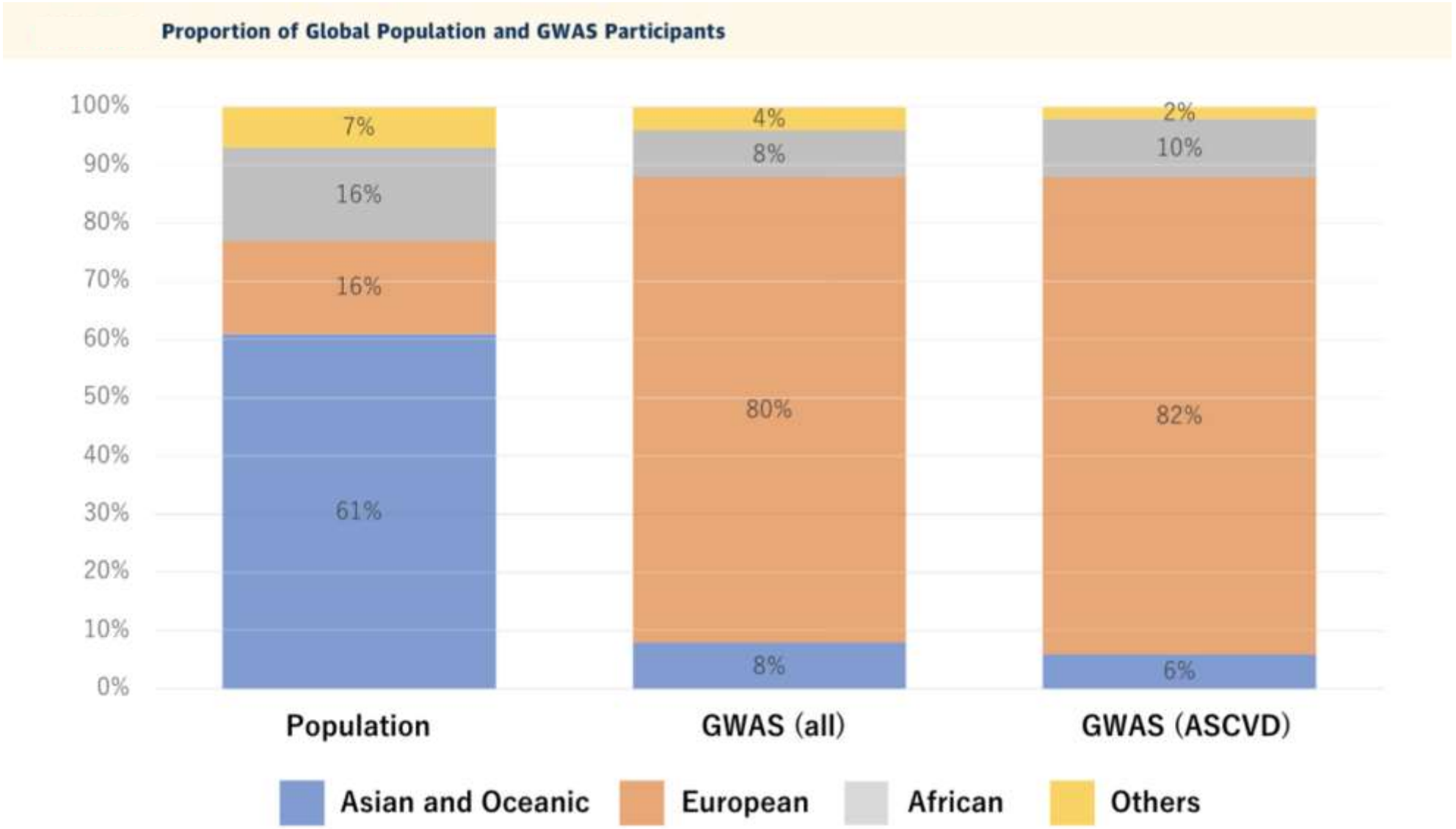
Add to discrimination of clinical ASCVD risk factors



There is debate whether addition of PRS to traditional risk scores significantly alters clinical decision-making in primary prevention patients



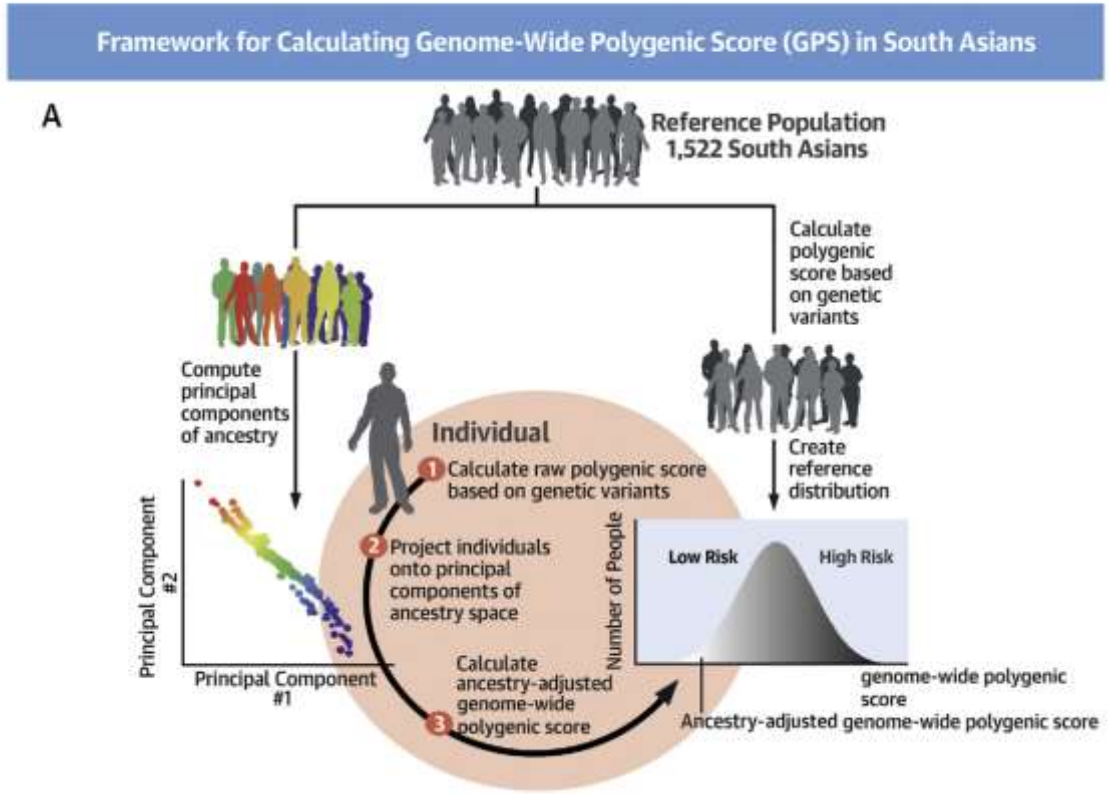
Participants from Asian and Oceanic backgrounds are significantly underrepresented in GWAS biobanks

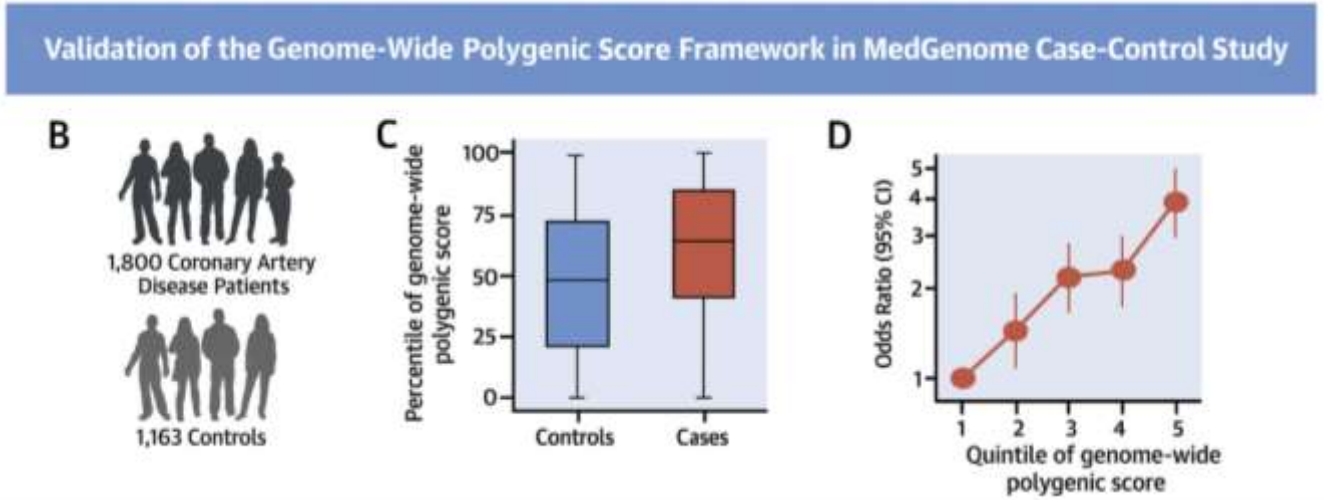


Tada, H. et al. J Am Coll Cardiol Asia. 2021 Dec 21;1(3):294-302

Ancestry-specific PRS are being developed and will be important tools for ensuring equitable access and use of genomic medicine

Development and Implementation of a Framework for Calculating Genome-Wide Polygenic Scores in South Asian Individuals





Compared with the middle quintile, risk for CAD was highest for those in the top 5% of the GPS_{CAD} distribution

Study	Odds ratio for CAD
UK Biobank South Asian	4.16
Bangladeshi (BRAVE)	2.46
Indian (GenomeAsia 100K project)	3.22

Wang M et al. J Am Coll Cardiol. 2020;76(6):703-714

29-year-old man presents to clinic for evaluation

Genetic testing revealed a pathogenic variant in *LDLR*
Cascade testing initiated for at-risk relatives

Rosuvastatin 40 mg QD
Ezetimibe 10 mg QD
Evolocumab (*PCSK9i*) q2weeks

Latest on treatment LDL-C = 74 mg/dL

Take Home Points

There are monogenic and polygenic contributions to premature coronary artery disease (CAD)

Carrying a disease-causing genetic variant for familial hypercholesterolemia increases CAD risk 3-4x

Familial hypercholesterolemia is massively underdiagnosed worldwide, and both clinical and genetic tools are essential to timely diagnosis and risk stratification

Polygenic risk scores for CAD have shown potential for risk stratification and prognostication, but there are many challenges to their implementation in routine clinical care

Thank you!

AMERICAN COLLEGE of CARDIOLOGY

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