7th Advances in Heart Failure 2024
10 e 11 de Outubro
FACULDADE DE MEDICINA DA UNIVERSIDADE DO PORTO

Fatores de risco não modificáveis para a IC: Que caminho para uma abordagem personalizada e precoce? GENÉTICA

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CINTESIS
RISE Health Research Network From the Lab to the Community

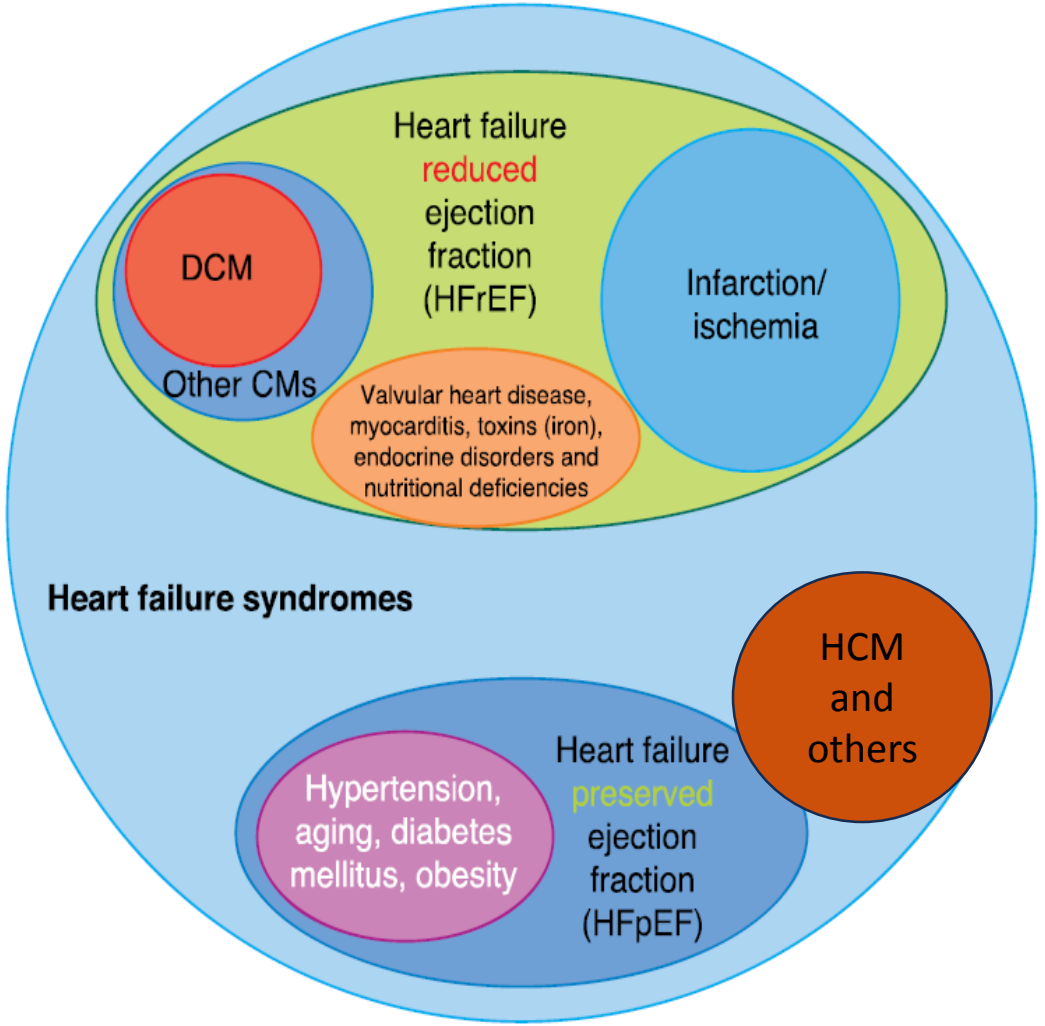
Introduction

- **Heart failure (HF)** affects globally 40 million people and is a major cause of mortality worldwide.

- In Europe:
  - Incidence: 30/10 000 person-years in all age-groups; 50/10 000 person-years in adults
  - Prevalence: 1-3% of adults

- **In Portugal:**
  - Prevalence: 16.54% in adults over 50 years

- **High disease burden and costs**



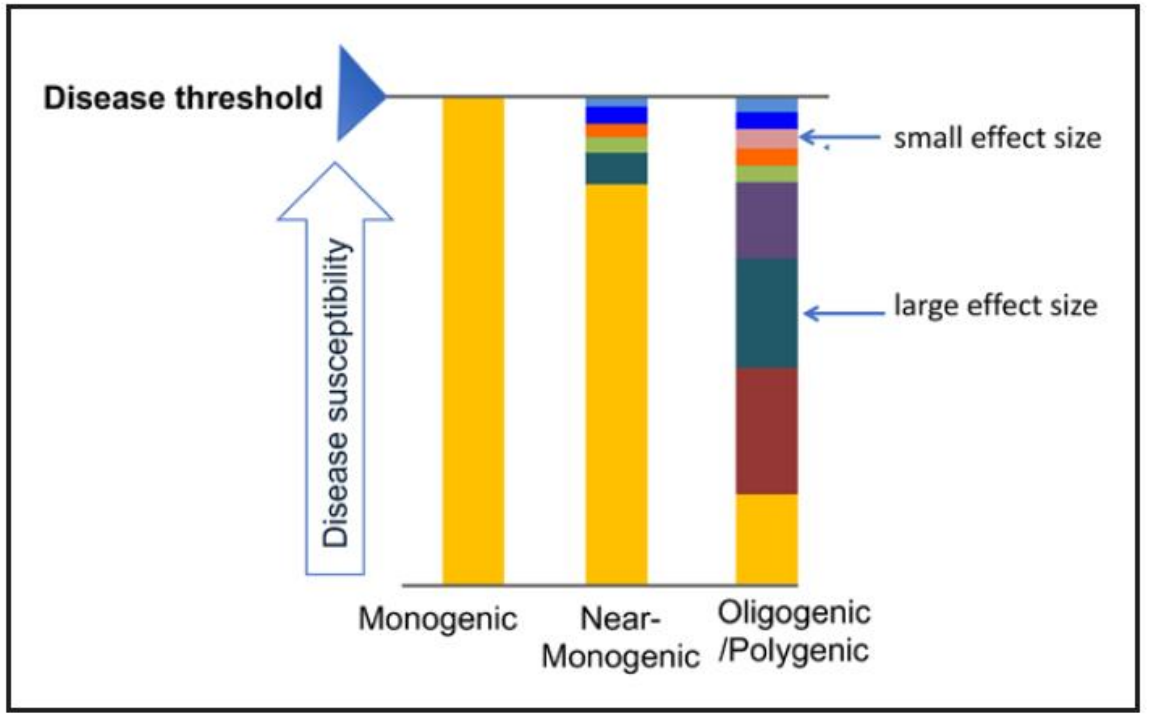
Tayal U et al. Genome Medicine 2017; 9:20

McDonagh TA, Eur Heart J 2021
Borlaug BA, JACC 2023
Kittleson MM, JACC 2023
PORTHOS study

Genetics in cardiovascular diseases

- **Mendelian genetic** in which **one gene** is associated with the disease, is characterized by **locus and allelic heterogeneity** and highly **variable** intra- and interfamilial **expressivity** with **incomplete/age-related clinical penetrance** (result of modifier genes, epigenetic effects, posttranscriptional and post-translational modifications, and environmental effects)

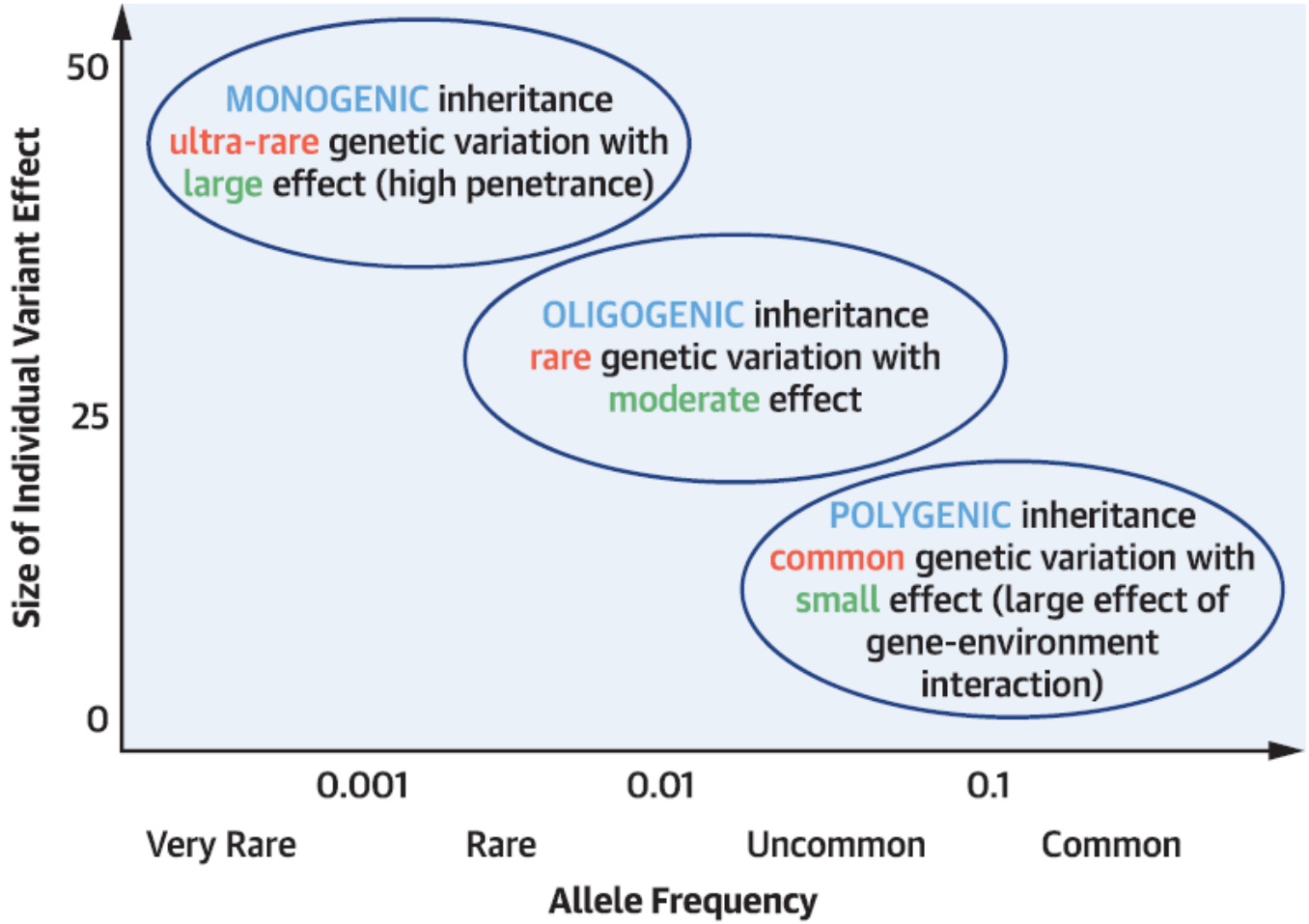
- **Genetic polymorphisms (SNPs)** modulate the maladaptive pathophysiological response to pathophysiological stressors, disease evolution and the response to therapy, with small effect size.



Cerrone M, Circulation 2019

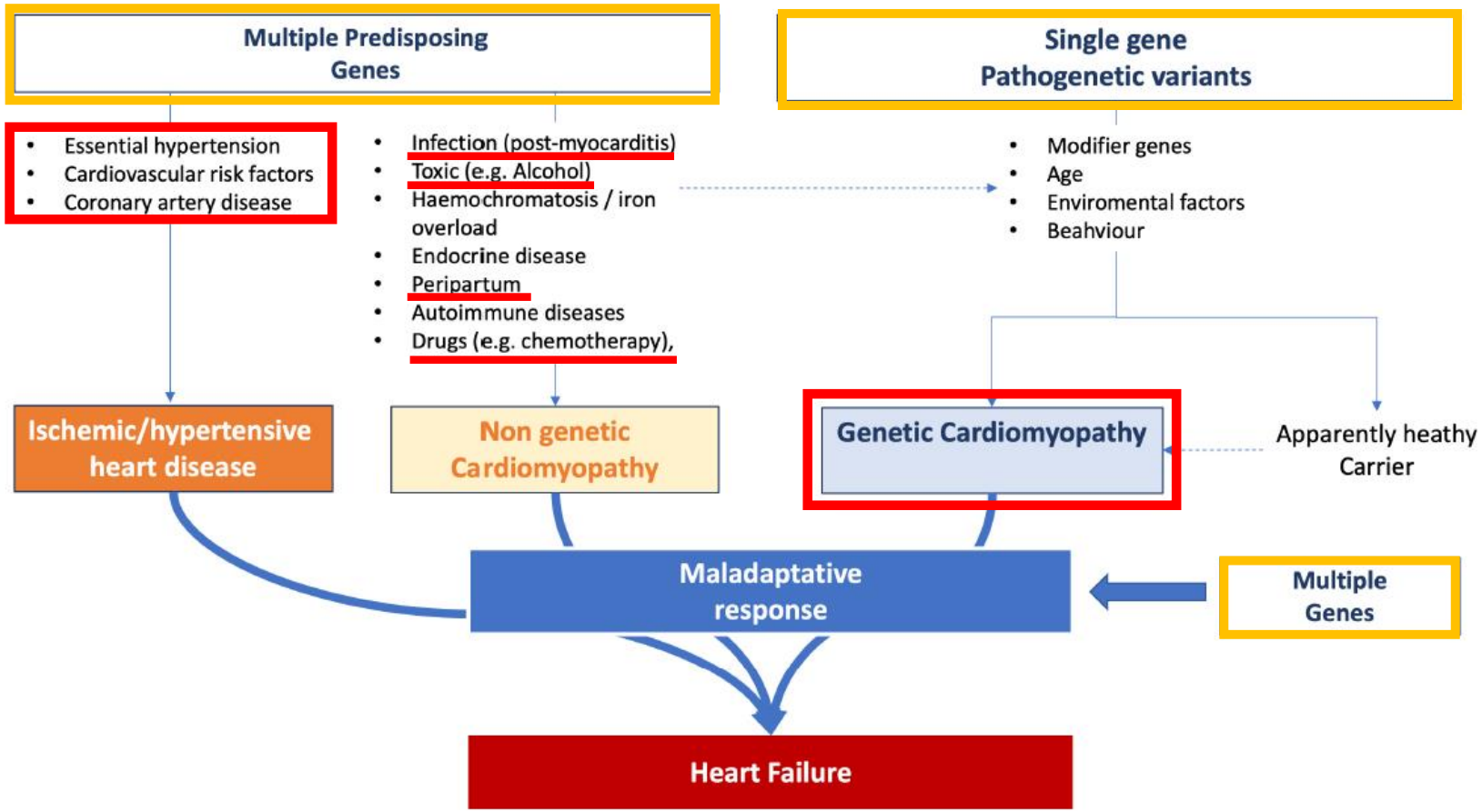
Jacoby D et al. Eur Heart J 2012; 33:296-304
Watkins H et al. NEJM 2011; 364:1643-56

Genetics in cardiovascular diseases



Semsarian C et al. JACC 2021; 77:2517-30

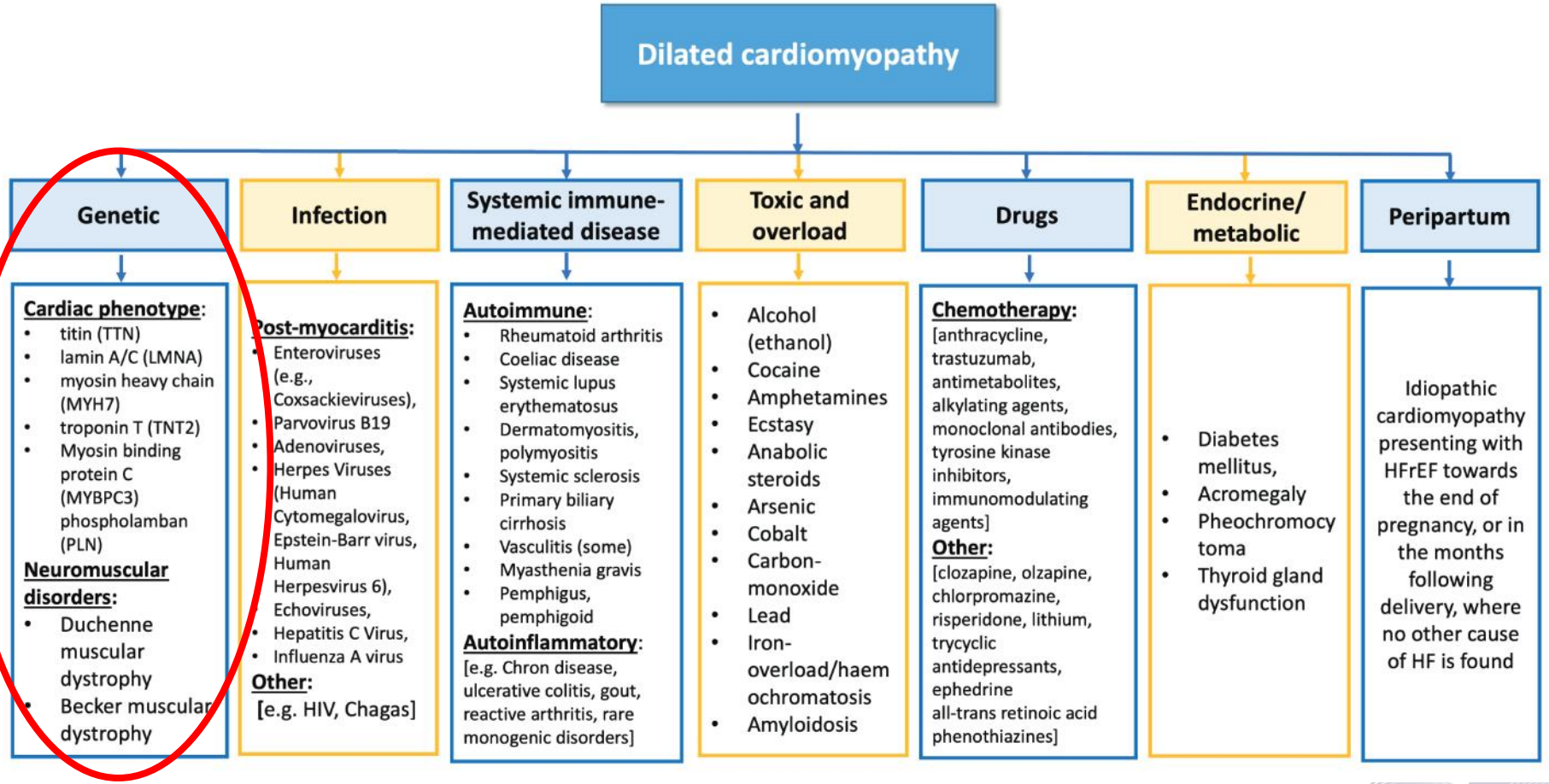
Influence of genetic background on heart failure onset and progression



Palmieri J et al. Int J Mol Sci 2023; 24:15221

Cardiomyopathies: Dilated Cardiomyopathy

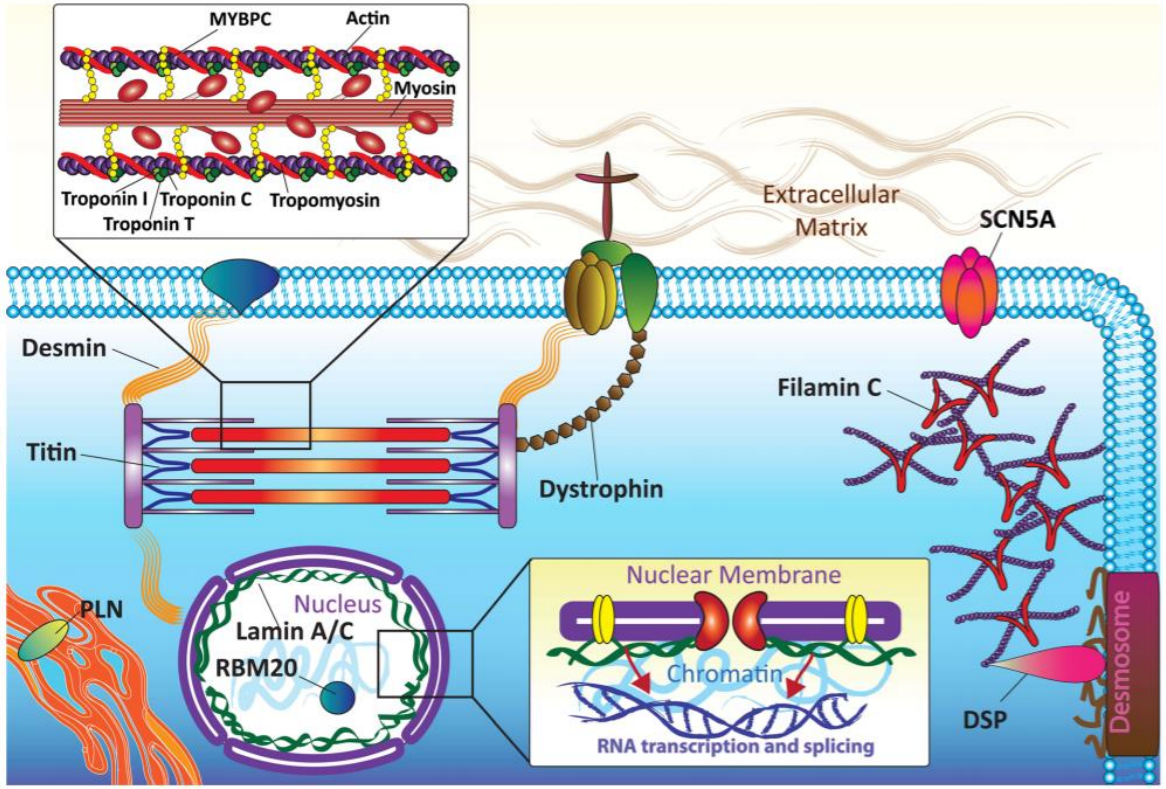
- DCM has an estimated prevalence of 2:500 and is a leading cause of heart transplant



Hershberger RE et al. Nat Rev Cardiol 2013; 10:531-47

Seferovic PM et al. Eur J Heart Fail 2019; 21: 553-76

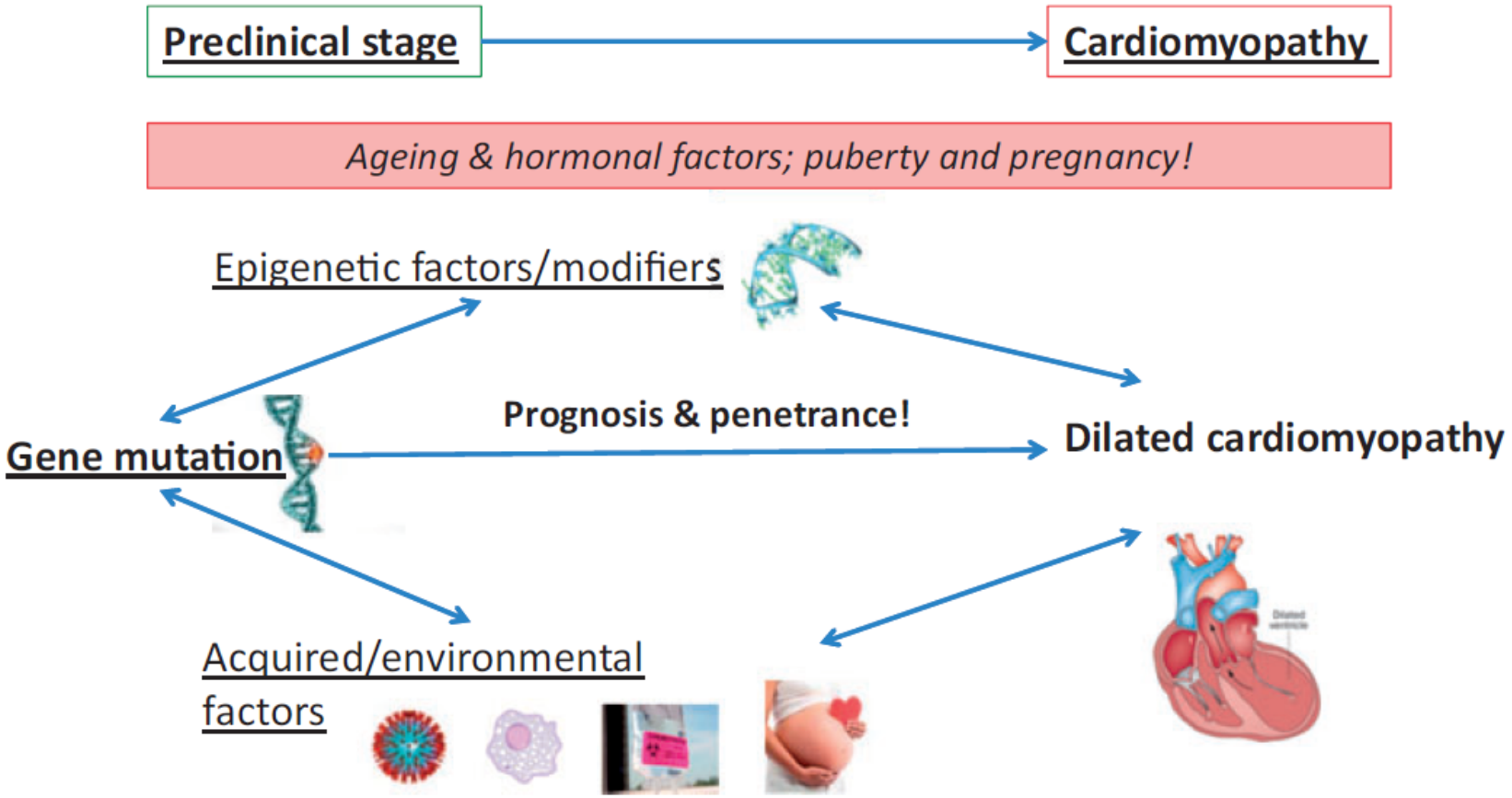
Genetic Dilated Cardiomyopathy



Sarcomere	ACTC	Actin		
	MYH6	a-myosin heavy chain		
	MYH7*	**b-myosin heavy chain**	**Autosomal Dominant**	**4% Familial DCM**
	MYPN	**Myopalladin**	**Autosomal Dominant**	**2% Familial DCM**
	MYBPC3	**Myosin-binding protein C**	**Autosomal Dominant**	**2% Familial DCM**
	TNNT2*	**Troponin T**	**Autosomal Dominant**	**2% Familial DCM**
	TNNC1	Troponin C		
	TNNI3*	Troponin I		
	TPM1	a-tropomyosin		
Cytoskeleton	ACTN2	a-actinin 2		
	SGC	sarcoglycan		
	CAV3	Caveolin		
	LDB3	Cypher/ZASP		
	SYNM	Desmulin		
	DMD	Dystrophin	X-linked	
	FKTN	Fukutin		
	ILK	Integrin-linked kinase		
	VCL	Metavinculin		
	NEXN	Nexilin		
	TTN	**Titin**	**Autosomal Dominant**	**20-25% Familial DCM**
Sarcoplasmatic	**PLN**	**Phospholamban**	**Autosomal Dominant**	**1% Familial DCM**
Reticulum	RYR2	Ryanodine receptor 2		
Ion Channel	**SCN5A**	**Sodium channel type V**	**Autosomal Dominant**	**2% Familial DCM**
	ABCC9	Sulfonylurea receptor 2A		
Mitochondria	CPT2	Carnitine palmitoyltransferase 2	Mitochondrial	
	mtDNA	Mitochondrial respiratory chain	Mitochondrial	
	TAZ/G4.5	Tafazin		
Heat Shock Protein	BAG3	BaCL2-associated athanogene 3		
Nuclear Membrane	**LMNA**	**Lamin A/C**	**Autosomal Dominant**	**6% Familial DCM**
	TMPO	Thymopoietin		
	EMD	Emerin		
Cell Nucleus	ANKRD1	Cardiac ankyrin repeat protein		
	EYA4	Eyes absent 4		
	NFKB1	NF-kappa B1		
	PRDM16	PR domain-containing 16		
	ZBTB17	Zinc finger and BTB domain-containing protein 17		
	RBM20	**RNA-binding protein 20**	**Autosomal Dominant**	**2% Familial DCM**
Desmosome	DES	Desmin		
	DSC2	Desmocollin 2		
	DSG2	Desmoglein 2		
	DSP	Desmoplakin		
	PKP2	Plakophilin 2		
Extracellular matrix	LAMA2	Laminin-a-2		
	LAMA4	Laminin-a-4		

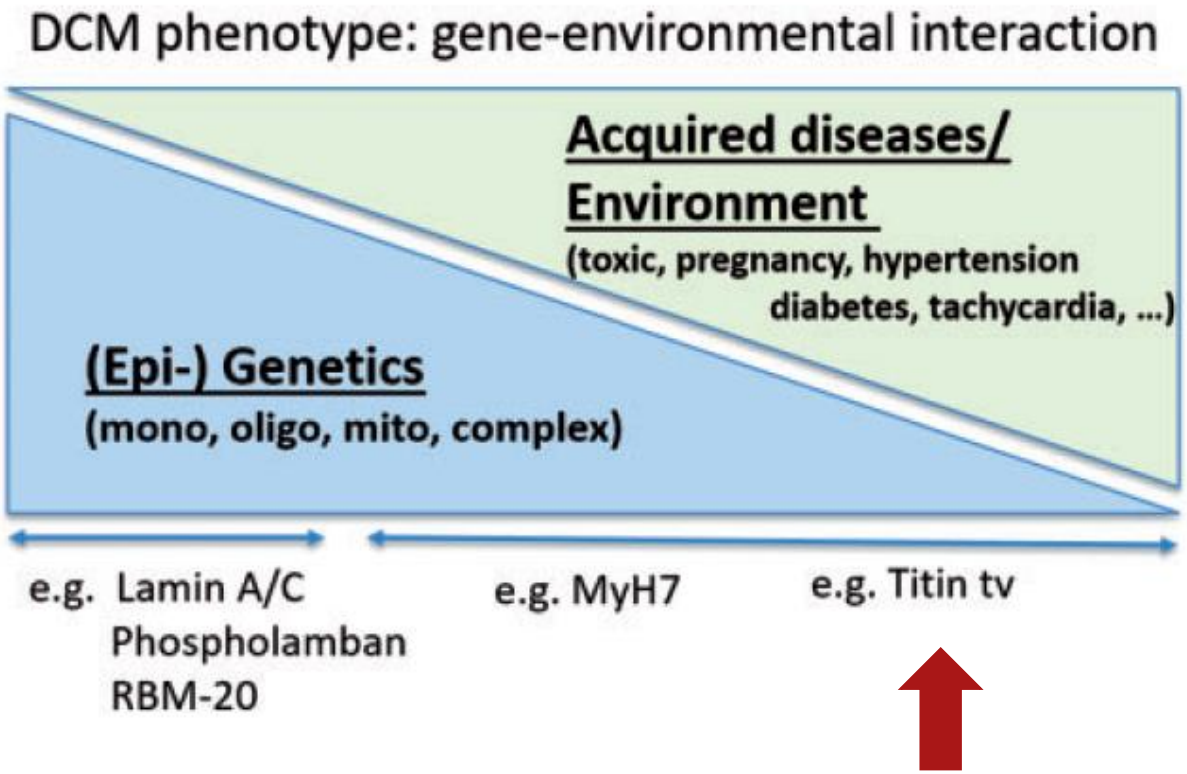
Paldino A et al. Curr Cardiol Rep 2018; 20:83

Dilated Cardiomyopathy



Bondue A et al. Cardiovasc Res 2018; 114:1287-303

Dilated Cardiomyopathy



Bondue A et al. Cardiovasc Res 2018; 114:1287-303

Shared Genetic Predisposition in Peripartum and Dilated Cardiomyopathies

Ware JS et al. NEJM 2016; 374:233-41

Genetic Etiology for Alcohol-Induced Cardiac Toxicity

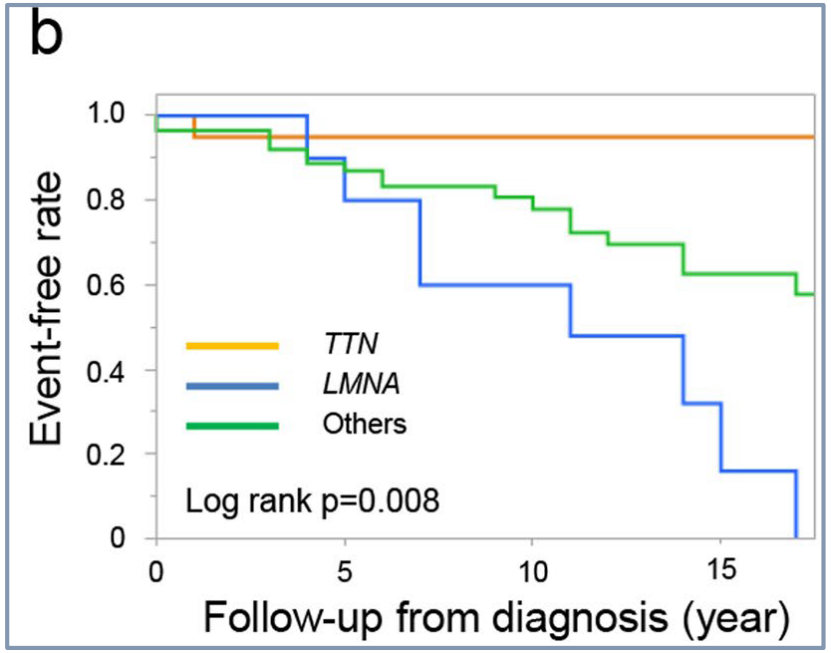
Ware JS et al. JACC 2018; 71:2293-302

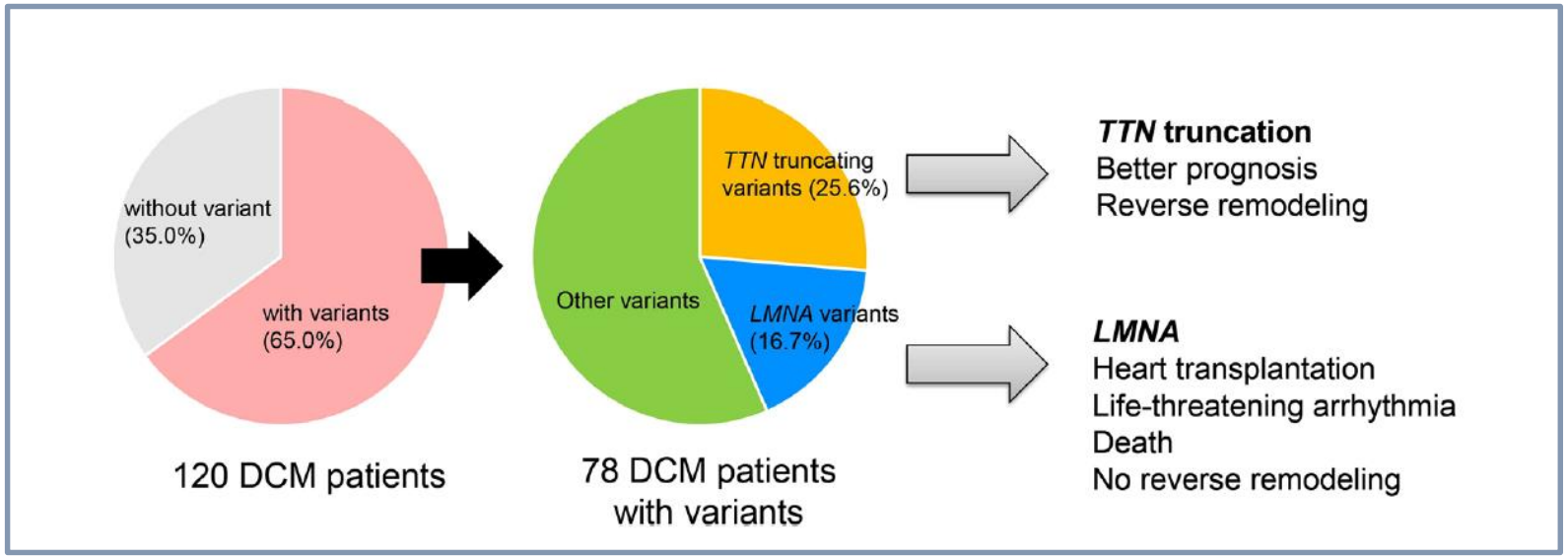
Genetic Variants Associated With Cancer Therapy–Induced Cardiomyopathy

Garcia-Pavia P et al. Circulation 2019; 140:31-41

Dilated Cardiomyopathy – prognosis and left ventricular reverse remodeling

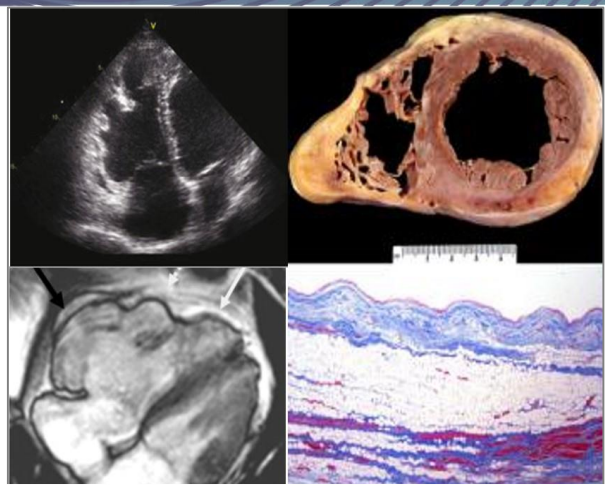
- ***TTN*tv** carriers have better prognosis and more reverse remodeling than ***LMNA*** variants carriers



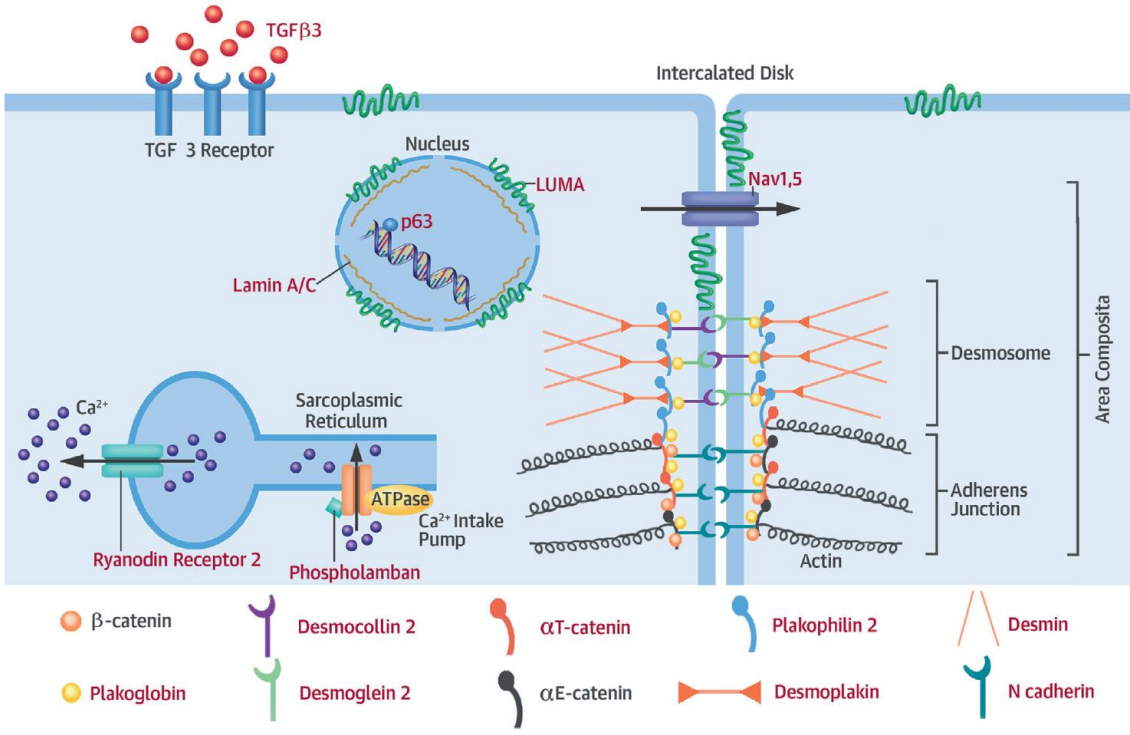


Bondue A et al. Cardiovasc Res 2018; 114:1287-303

Arrhythmogenic (right ventricular) cardiomyopathy

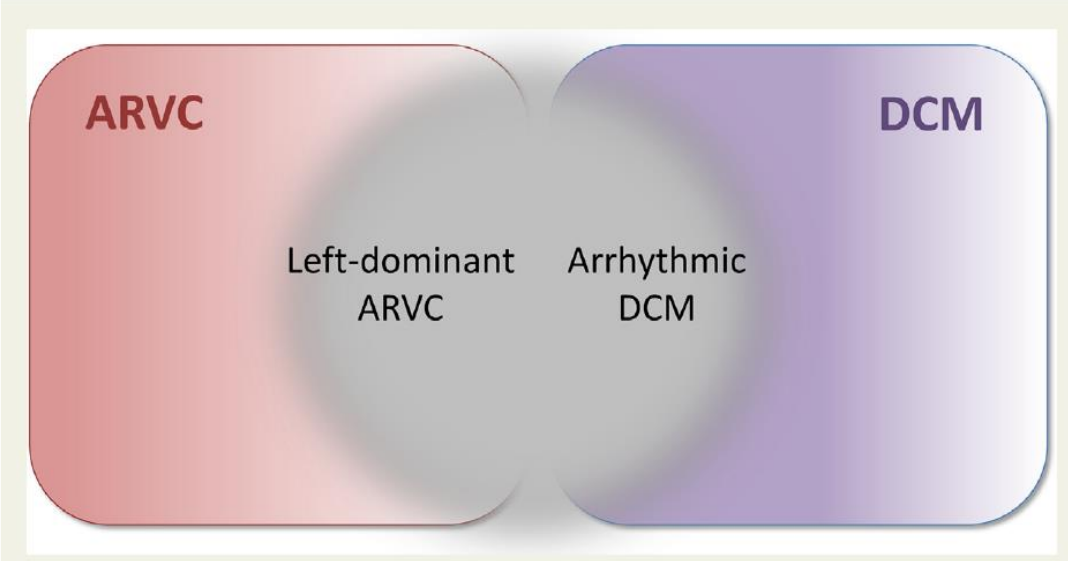


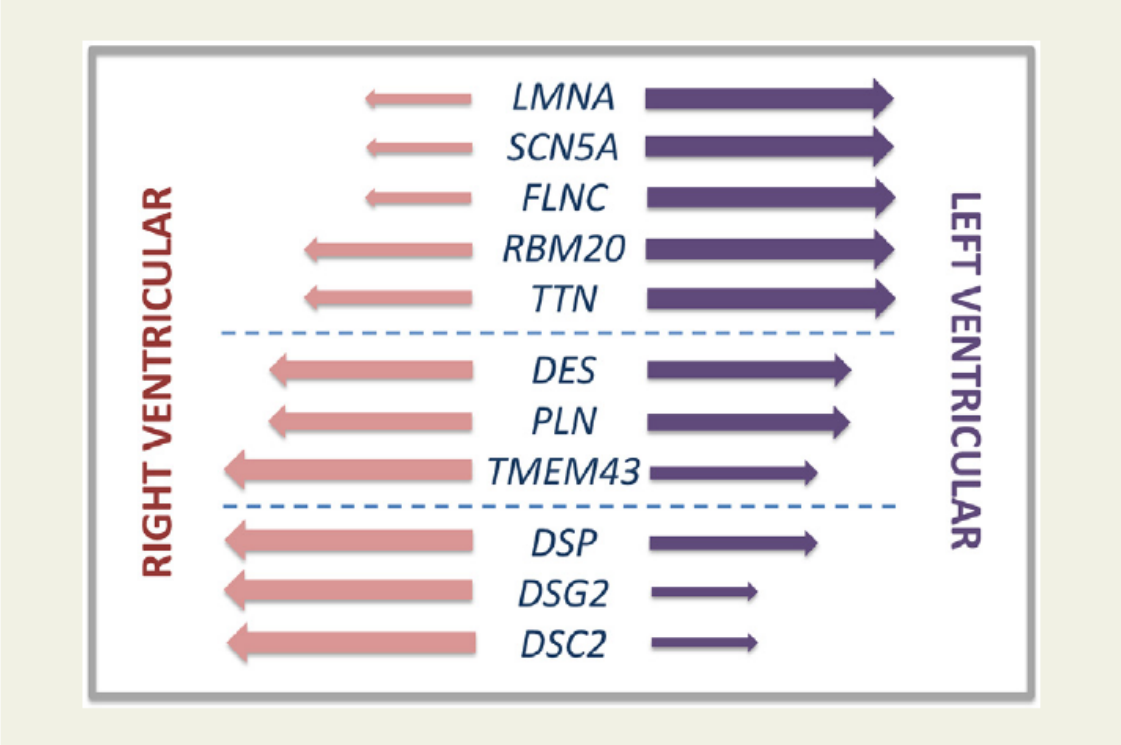
- Prevalence 1/2000-5000; Males>Females (3:1)
- Progressive fibrofatty replacement of ventricular myocardium, apoptosis and inflammation
- Frequent sustained ventricular arrhythmias and high risk of sudden cardiac death (10% per year); progressive ventricular dysfunction and heart failure (later in the course of the disease)



Gerull B et al. Curr Heart Fail Rep 2021; 18:378-90
James CA et al. Eur Heart J 2020; 41:1393-400
Gandjbakhch E et al. JACC 2018; 72:784-804

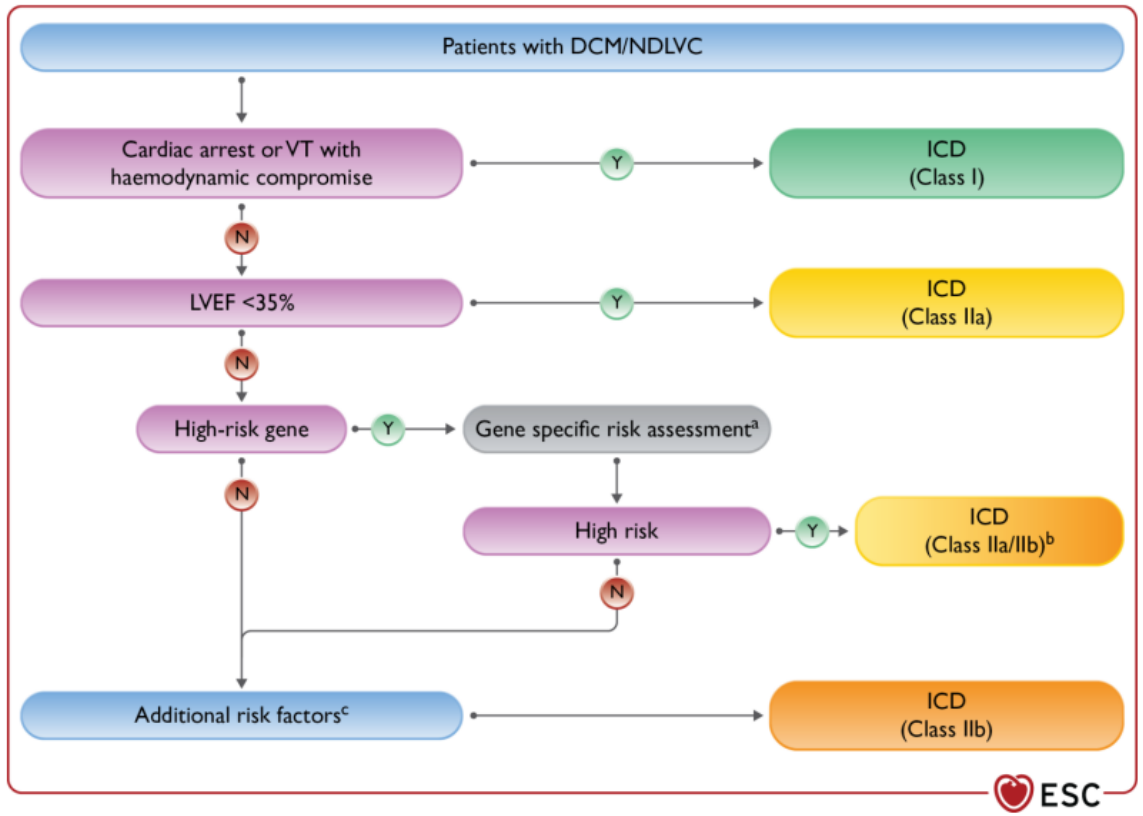
Arrhythmogenic cardiomyopathies





Peters S et al. Heart Lung Circ 2019; 28:31-38

Prevention of sudden cardiac death



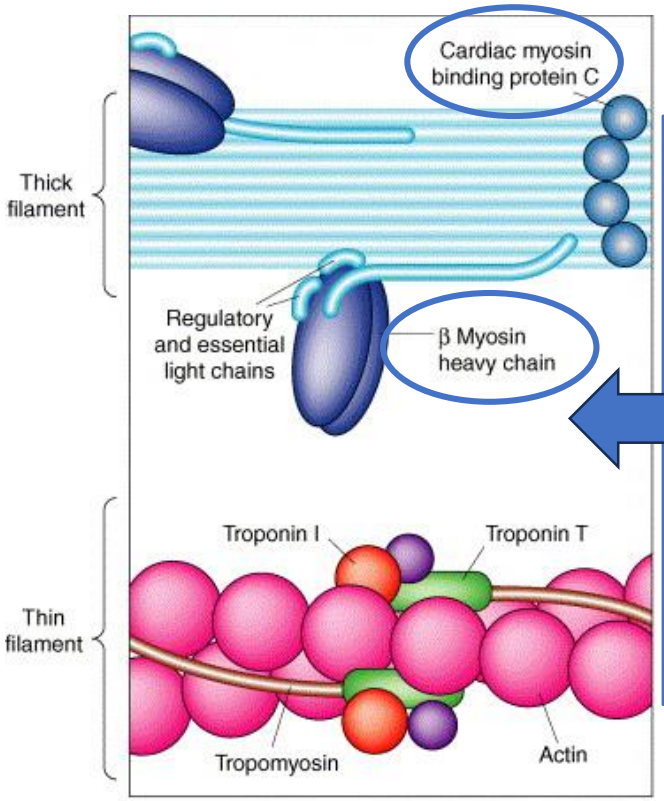
Additional risk factors: include syncope, LGE presence on CMR

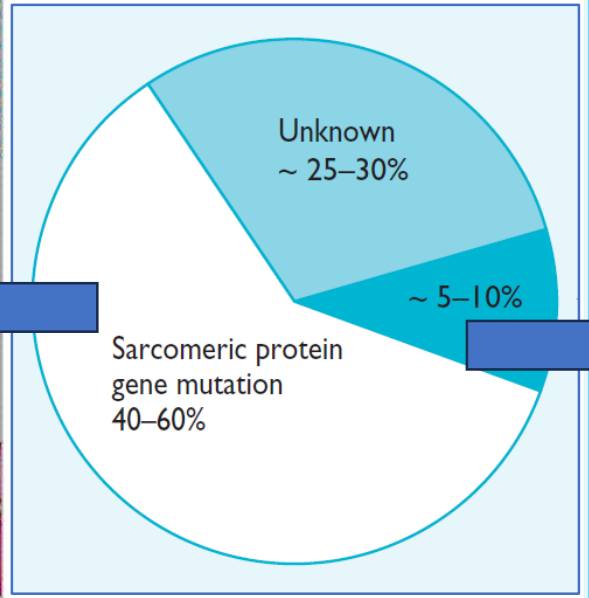
Primary prevention		
An ICD should be considered to reduce the risk of sudden death and all-cause mortality in patients with DCM, symptomatic heart failure, and LVEF ≤35% despite >3 months of OMT.	IIa	A
The patient's genotype should be considered in the estimation of SCD risk in DCM.	IIa	B
An ICD should be considered in patients with DCM with a genotype associated with high SCD risk and LVEF >35% in the presence of additional risk factors.	IIa	C
An ICD may be considered in selected patients with DCM with a genotype associated with high SCD risk and LVEF >35% without additional risk factors.	IIb	C
An ICD may be considered in patients with DCM without a genotype associated with high SCD risk and LVEF >35% in the presence of additional risk factors.	IIb	C

Gene	Annual SCD rate	Predictors of SCD
LMNA	5–10%	Estimated 5-year risk of life-threatening arrhythmia using LMNA risk score https://lmna-risk-vta.fr
***FLNC*-truncating variants**	5–10%	LGE on CMR LVEF<45%
TMEM43	5–10%	Male Female and any of the following: LVEF <45%, NSVT, LGE on CMR, >200 VE on 24h Holter ECG
PLN	3–5%	Estimated 5-year risk of life-threatening arrhythmia using *PLN* risk score https://plnriskcalculator.shinyapps.io/final_shiny LVEF<45% LGE on CMR NSVT
DSP	3–5%	LGE on CMR LVEF<45%
RBM20	3–5%	LGE on CMR LVEF<45%

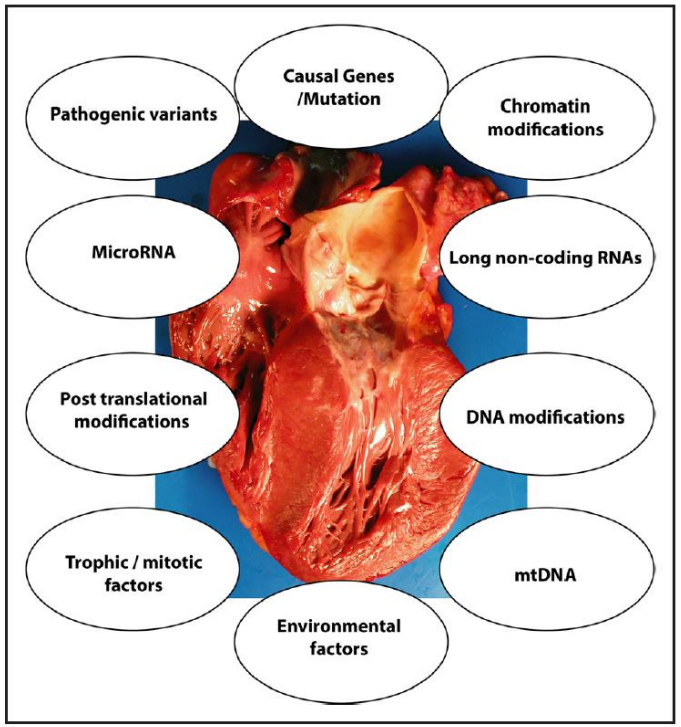
Arbelo E et al. Eur Heart J 2023; 44:3503-626

Hypertrophic cardiomyopathy





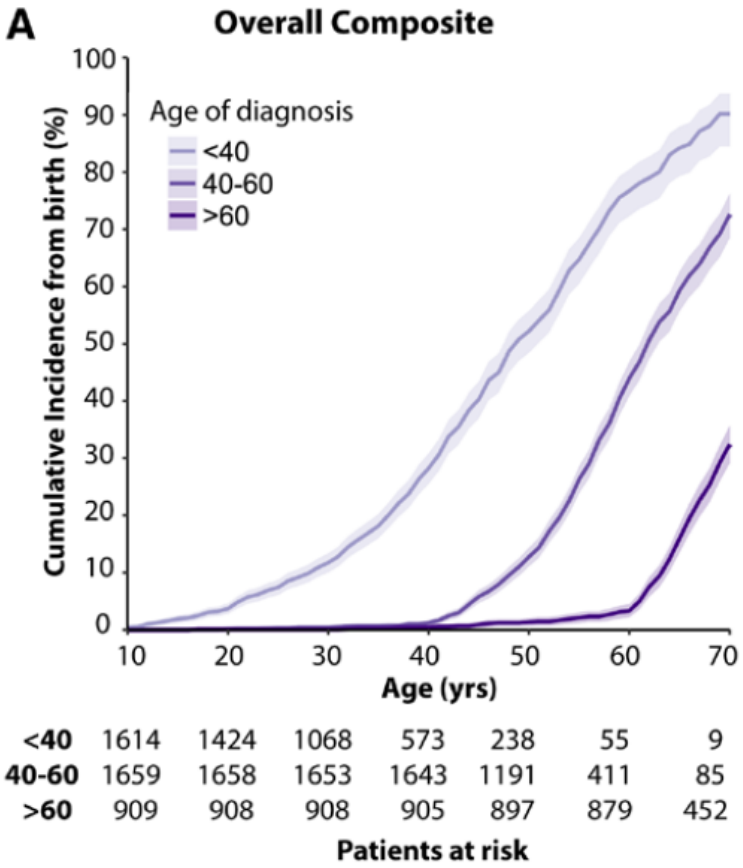
- **Inborn errors of metabolism**
  Glycogen storage diseases:
  - Pompe
  - Danon
- AMP-Kinase (PRKAG2)
- Carnitine disorders
- Lysosomal storage diseases
  - Anderson-Fabry
- **Neuromuscular diseases**
  - Friedreich's ataxia
  - FHL1
- **Mitochondrial diseases**
  - MELAS
  - MERFF
- **Malformation Syndromes**
  - Noonan
  - LEOPARD
  - Costello
  - CFC
- **Amyloidosis**
  - Familial ATTR
  - Wild type TTR (senile)
  - AL amyloidosis
- **Newborn of diabetic mother**
- **Drug-induced**
  - Tacrolimus
  - Hydroxychloroquine
  - Steroids

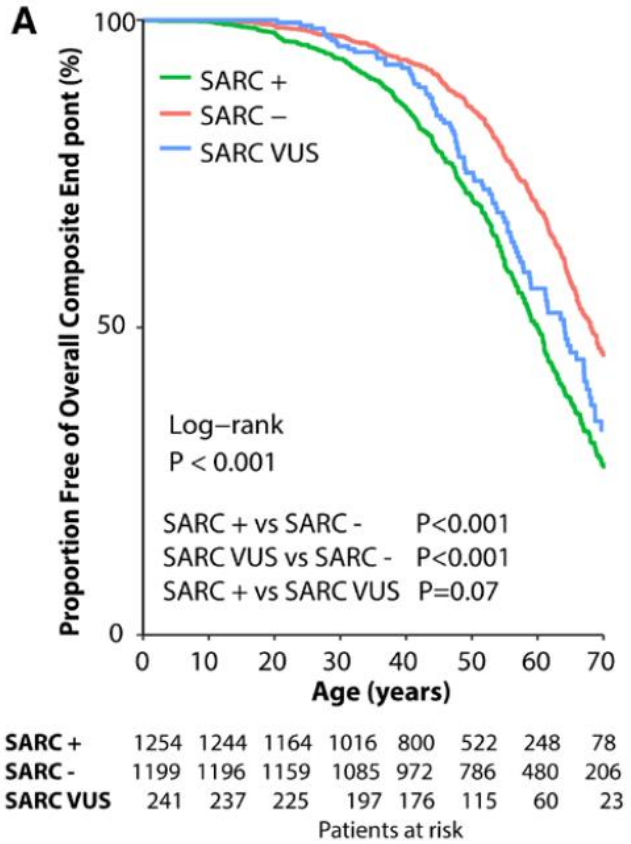


Elliot P et al. Eur Heart J 2014; 35:2733-79

Genotype and Lifetime Burden of Disease in Hypertrophic Cardiomyopathy

Insights From the Sarcomeric Human Cardiomyopathy Registry (SHaRe)



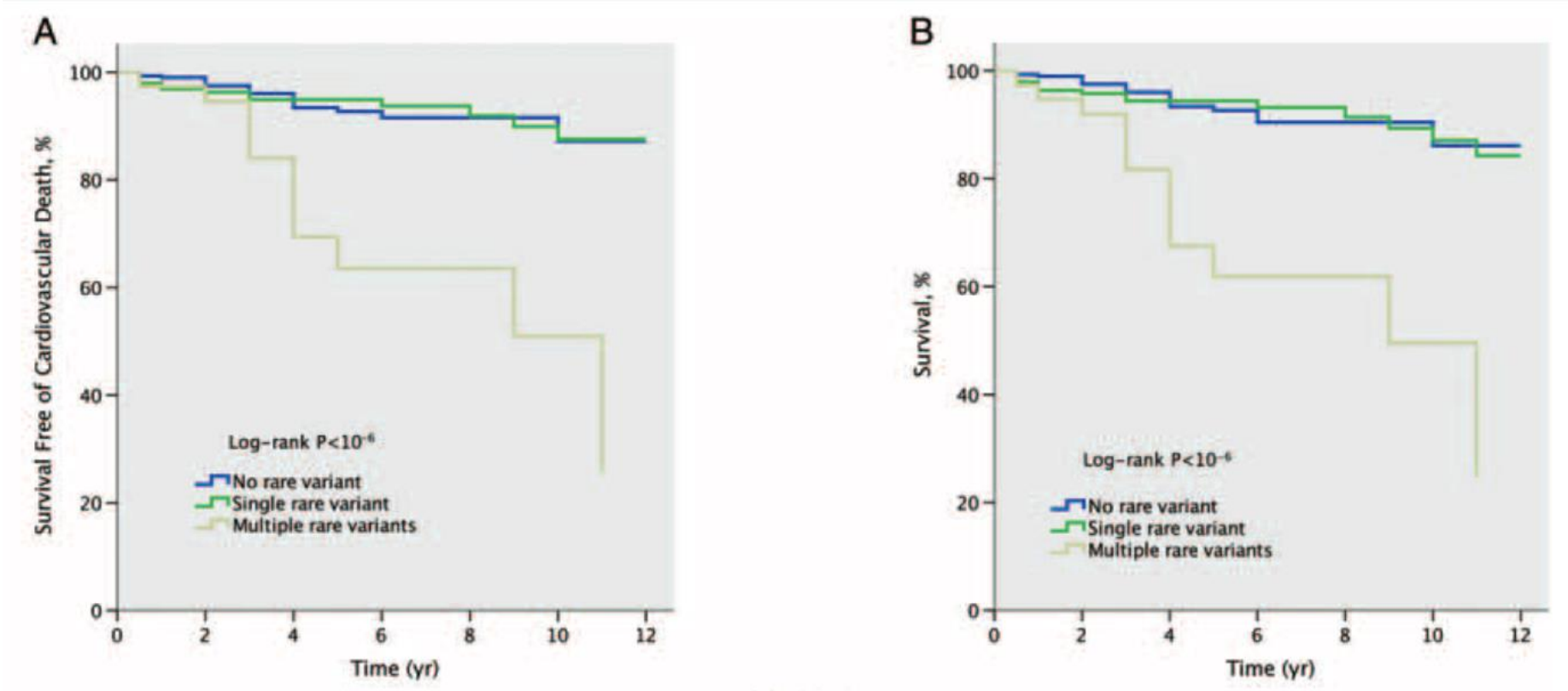


- Cumulative incidence of adverse end-points is higher in patients with earlier diagnosis
- Patients without sarcomeric variants have better prognosis than patients with VUS or pathogenic variants in sarcomeric genes.

Ho CY et al. Circ 2018;138:1387-98

Malignant effects of multiple rare variants in sarcomere genes on the prognosis of patients with hypertrophic cardiomyopathy

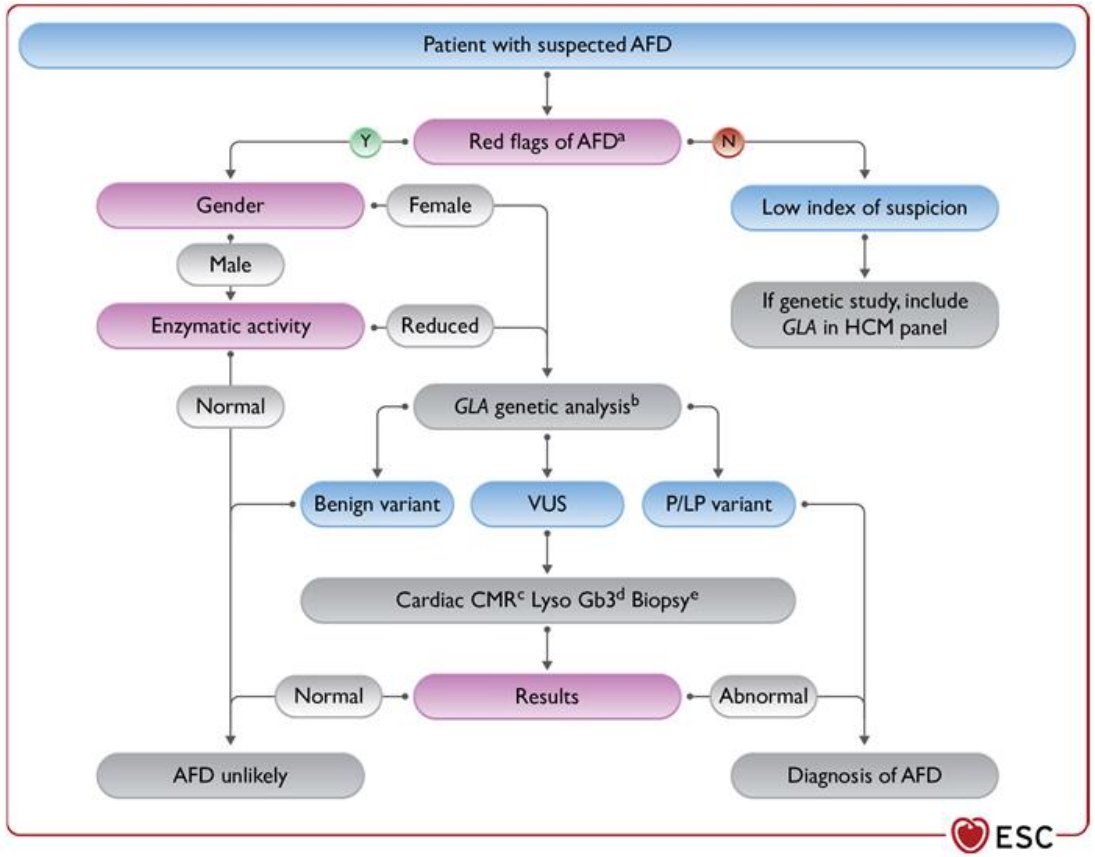
- Up to 5% of HCM patients present with multiple genetic variants



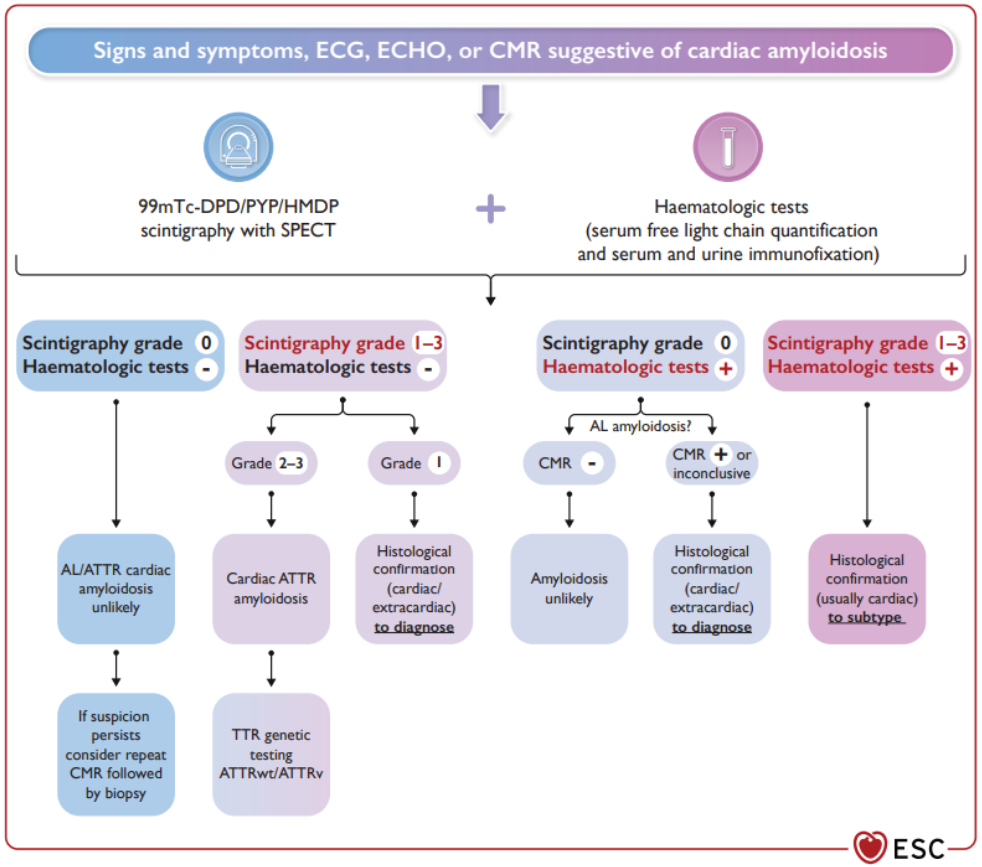
Wang J et al. Eur J Heart Fail 2014; 16:950-7

Hypertrophic cardiomyopathy: phenocopies with specific treatment

Anderson – Fabry Disease

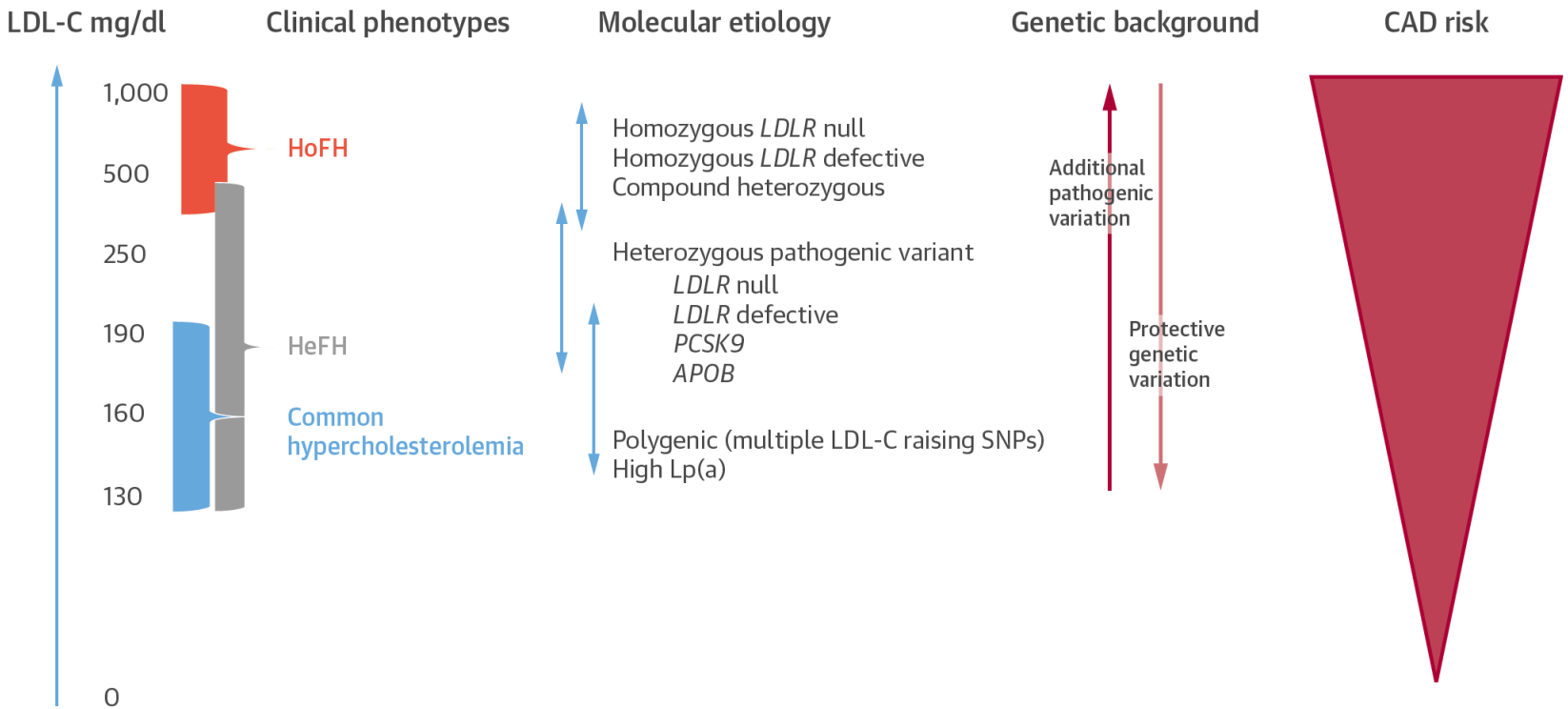


Cardiac amyloidosis (TTR)



Arbelo E et al. Eur Heart J 2023; 44:3503-626

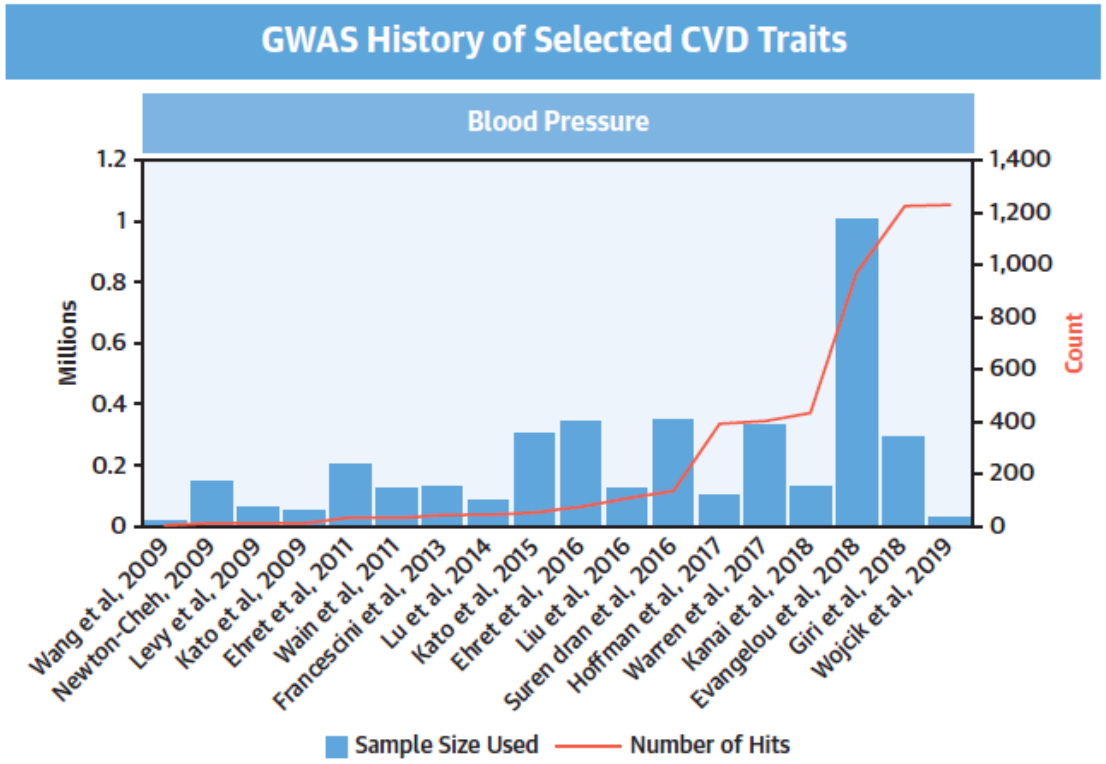
Cardiovascular risk factors and coronary disease: Familial Hypercholesterolemia



- Prevalence 1:220
- Potencially fatal, treatable and underdiagnosed
- Genetic testing:
  - Definite diagnosis
  - Proper treatment, earlier and increased adhesion
  - Familial screening
  - Better risk stratification

Sturm AC et al. JACC 2018; 72:662-80

Cardiovascular risk factors and coronary disease: Arterial hypertension



- Blood pressure is highly heritable, with heritable factors accounting for 30% to 50% of a given individual's blood pressure.
- There are more than 505 independent loci associate with one or more blood pressure traits.

Miller CL et al. JACC 2021; 77: 2531-50

(Premature) Coronary Disease

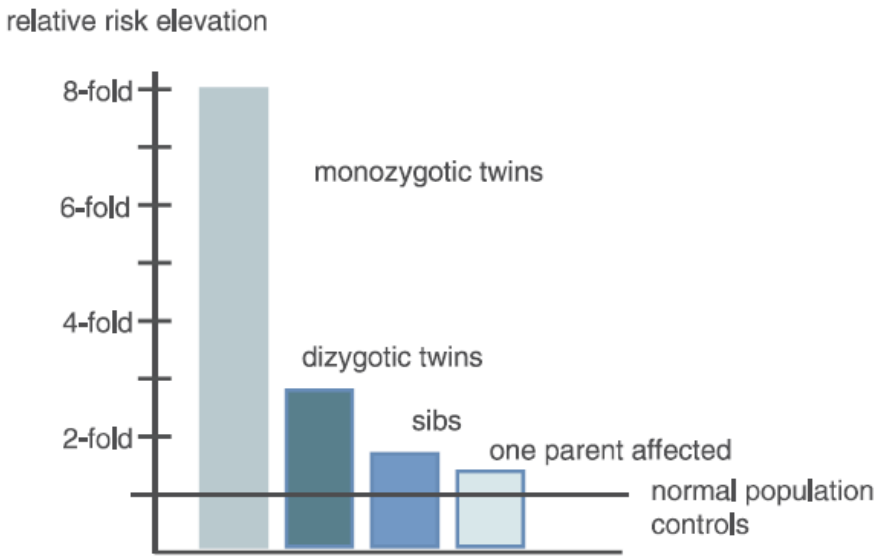
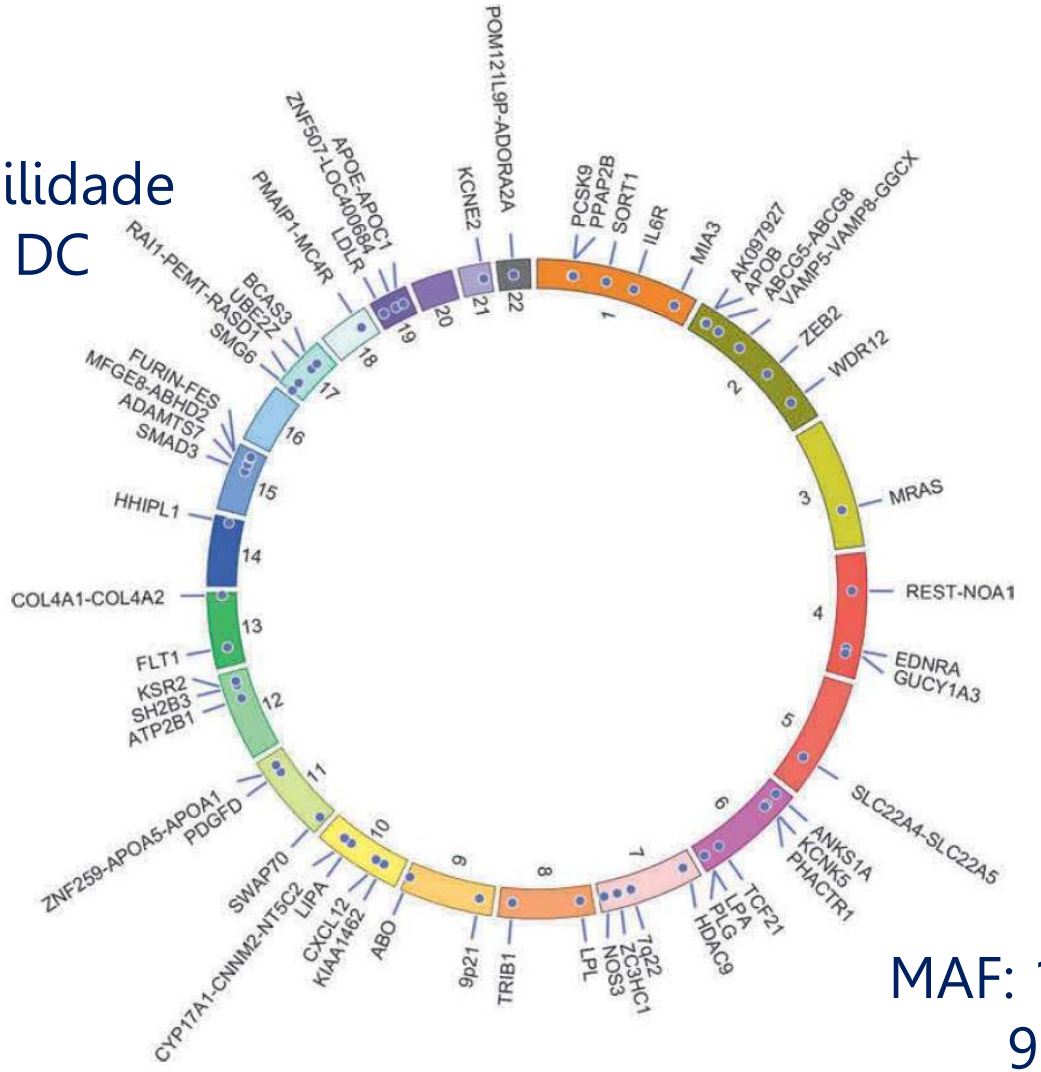


Fig. 22.1 The relative increase in the risk of myocardial infarction (MI)/coronary artery disease (CAD) is shown in relation to different familial backgrounds. The risk for monozygotic (MZ) and dizygotic (DZ) twins is based on the hypothesis that the partner twin died of MI at the age of 55 years

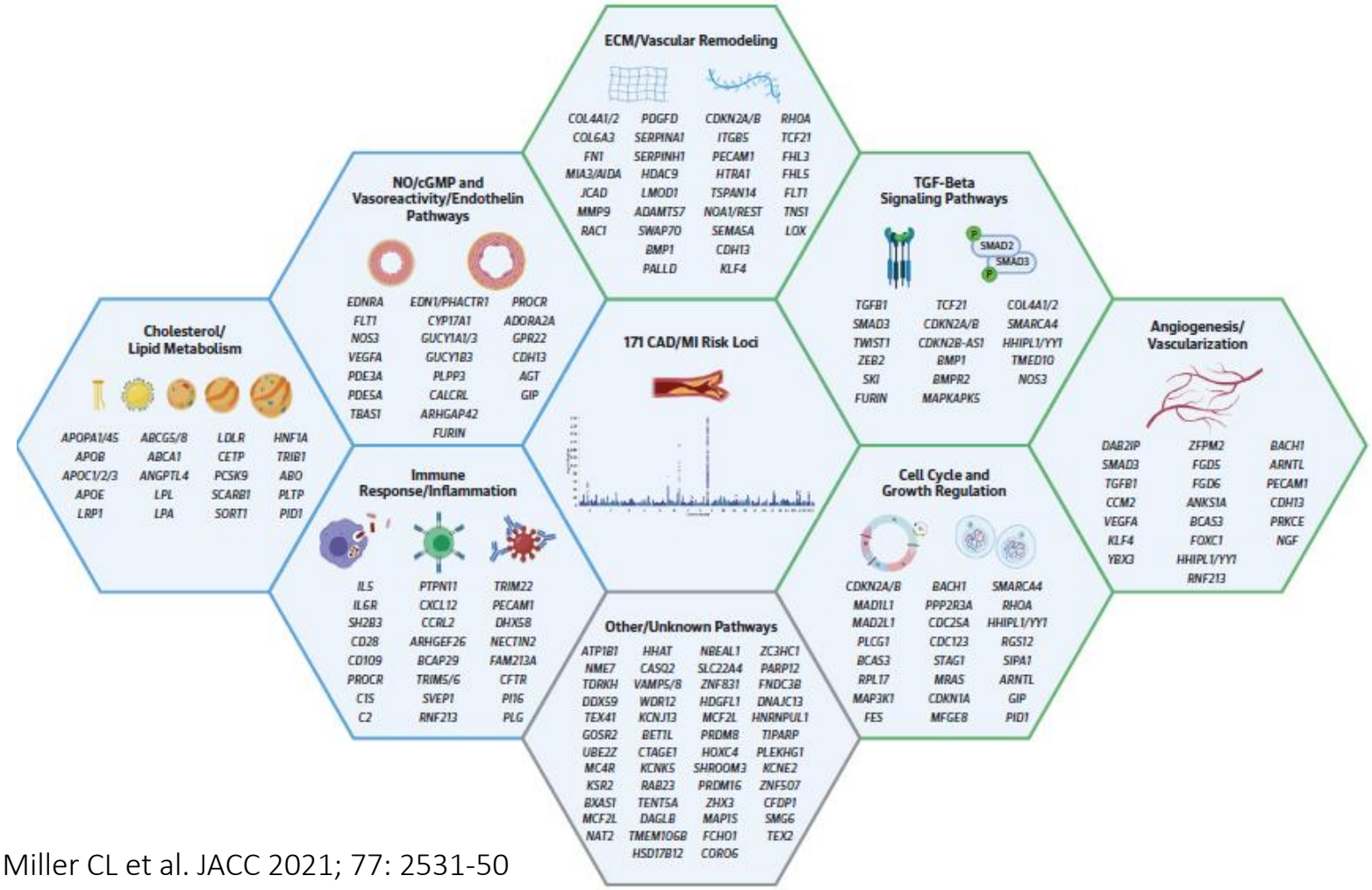
GWAS
~15%
hereditabilidade
de EAM e DC



MAF: 10-90%
OR: 1.05-1.30

Erdmann J, *Genetics of (Premature) Coronary Artery Disease* in Clinical Cardiogenetics 2016

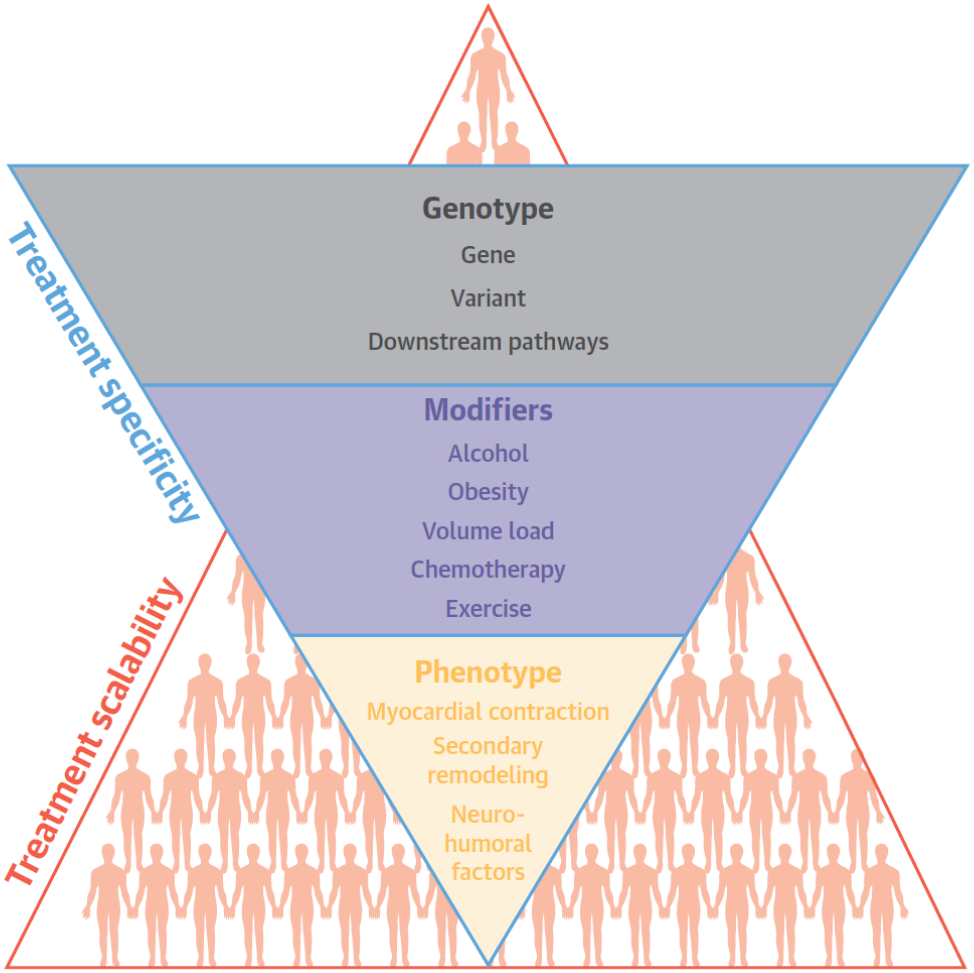
(Premature) Coronary Disease – Annotated Genes and Pathways Associated With CAD and/or MI



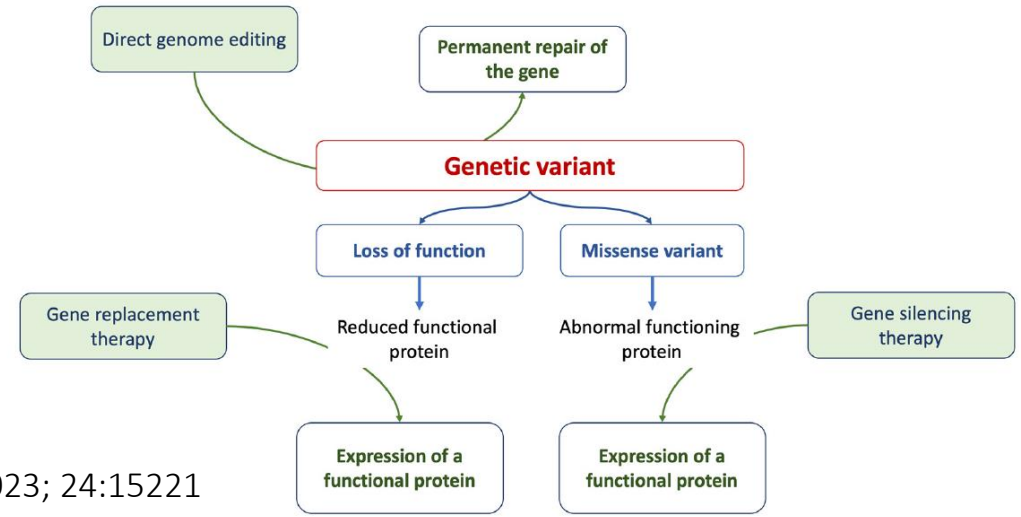
- There are at least 168 reported genome-wide significant loci and >400 suggestive loci associated with CAD causality
- **Polygenic risk scores**

Miller CL et al. JACC 2021; 77: 2531-50

Genotype–based therapy – Precision Medicine



- **Improvement of clinical consequences: improved sudden death risk stratification**
- **Target the molecular consequences of a specific gene mutation (ex. replacement therapies)**
- **Early implementation od preventive measures**
- **Address the genetic alteration**



Fatkin D et al. JACC 2019; 74:2921-38

Palmieri J et al. Int J Mol Sci 2023; 24:15221

Personalized and early approach

FOR THE PATIENT

- More refined diagnosis
- Individual risk assessment
- Preventive measures and lifestyle modifications (exercise and reproductive issues)
- Specific therapies

Personalized and early approach

FOR THE FAMILY

- Early diagnosis of the disease in asymptomatic

- Identifying at-risk family members
  - Genotype positive-phenotype negative family member need regular screening (individualized plans)
  - Early detection of the disease and management of incipient disease
  - Sports
  - Reproductive issues

- Genetic counseling and psychological support

TAKE-HOME MESSAGES

- Heart failure is a major health burden
- Up 30-40% might be attributable to genetic factors
- Knowledge of genetic background and gene-to-gene, epigenetics and ambiental interactions allows:

- Early diagnosis
- Improved individual risk assessment
- Possibility of targeted preventive measures (increased health monitoring, early therapeutic interventions, lifestyle modifications) and specialized diagnostic procedures and therapeutics
- Improved family management

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