La genetica nella stratificazione del rischio clinico della cardiomiopatia dilatativa

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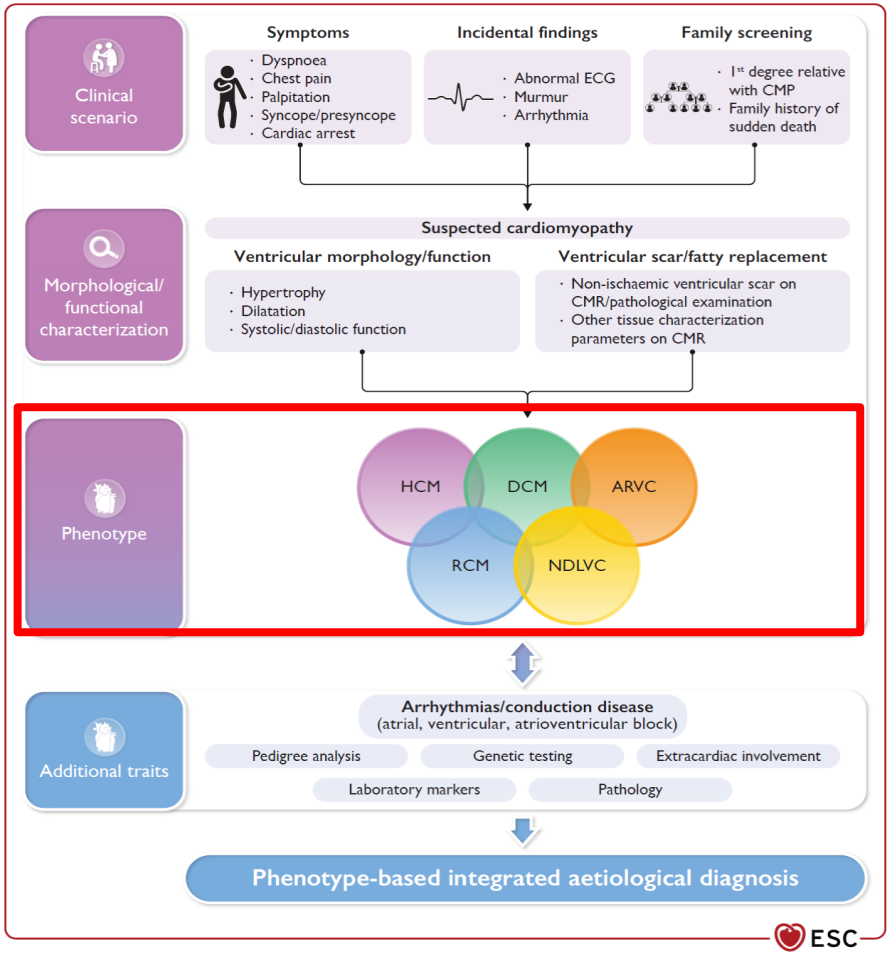
2023 ESC Guidelines for the management of cardiomyopathies

Developed by the task force on the management of cardiomyopathies of the European Society of Cardiology (ESC)

The cardiomyopathy mindset

Phenotype-centered diagnostic approach

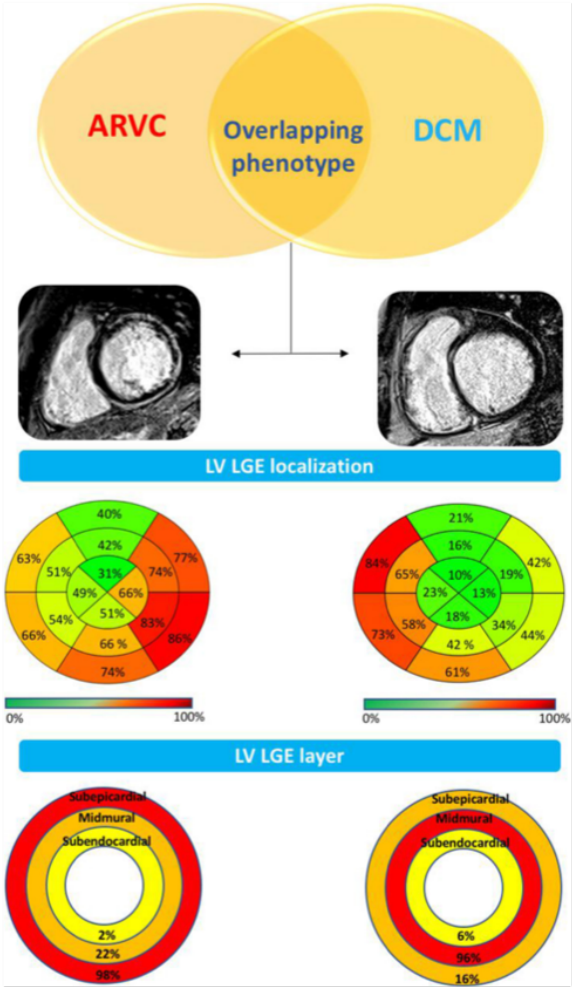


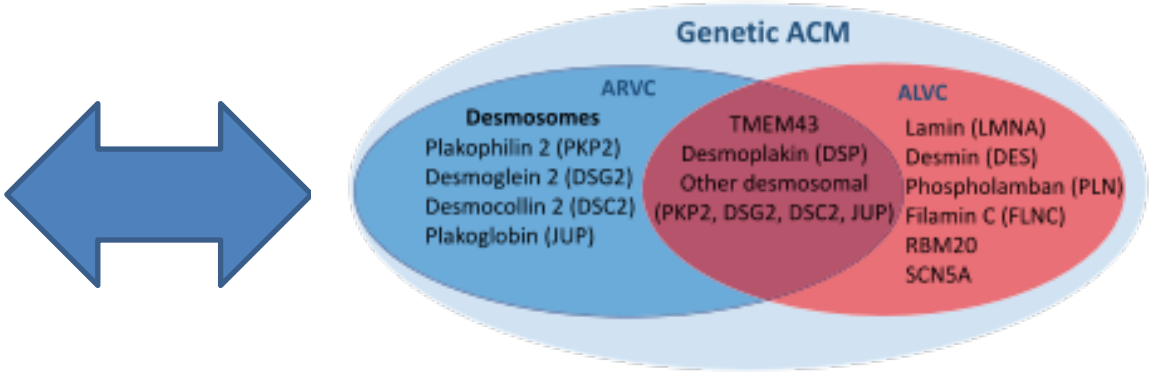
ESC European Society of Cardiology

European Heart Journal (2023) **00**, 1–124
https://doi.org/10.1093/eurheartj/ehad194

Arrhythmogenic left ventricular cardiomyopathy

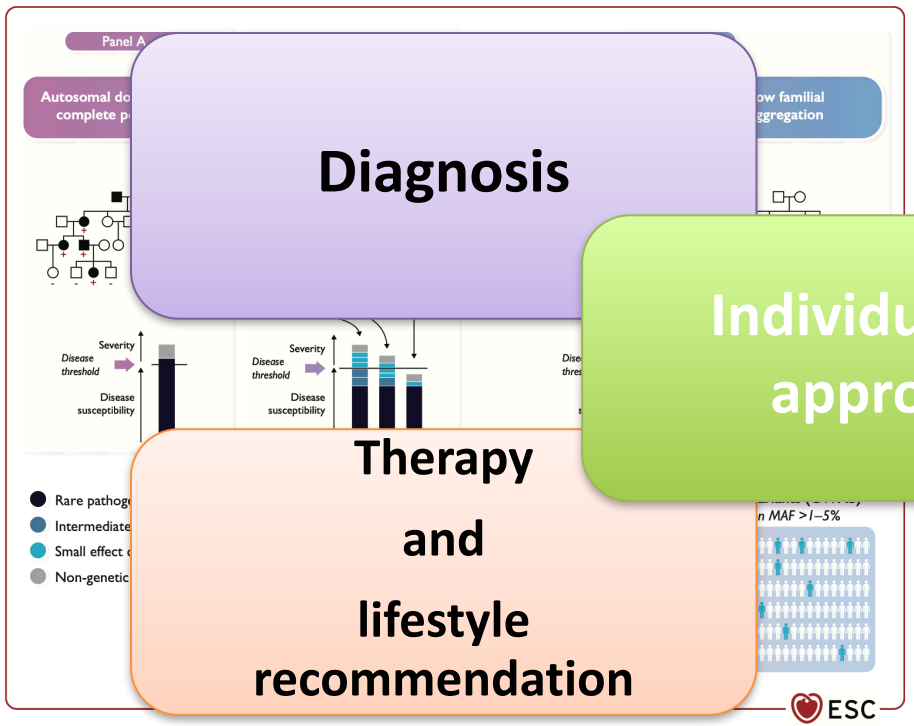
Domenico Corrado, Cristina Basso





Corrado D, Basso C. *Heart* 2021;**0**:1–11. doi:10.1136/heartjnl-2020-316944

Genetic testing and counselling in ESC 2023 guidelines



Diagnosis

Prognosis

Individualized approach

Therapy and lifestyle recommendation

Cascade family screening

•**Diagnosis:** for the affected individual, the diagnosis of cardiomyopathy is primarily made on the basis of a phen… However, with appropr…vill only be clinically actiona…ying borderline cases (e.g. wh…ut the clinician is not able to …ve phenocopy). Genetic testing …ticular cardiom…

…ide prognostic …is requiring more …hreshold for primary …

…**s may directly stratify choice of therapy. In addition to decisions on** …antation, an increasing number of treatments are either established or …ecular subtype of cardiomyopathy. In addition, with an increasingly …nipulation of the genome, further waves of therapies aiming to replace, …hies are anticipated once …

…agement for an affected… …n inheritance patterns and the… …ment of risk; e.g. through…

For rela…

•Cardio… …ariability, therefore it is very dif… …g cardiomyopathy. A normal c… …pathy on initial evaluation may require long-term longitudinal surveillance. Genetic testing can eliminate this uncertainty: an individual who does not carry the genetic variant proved to be respo… in their family can be confidently reassured and discharged without surveillance, wh… who carries a disease-causing variant can be followed closely, and potentially treate…

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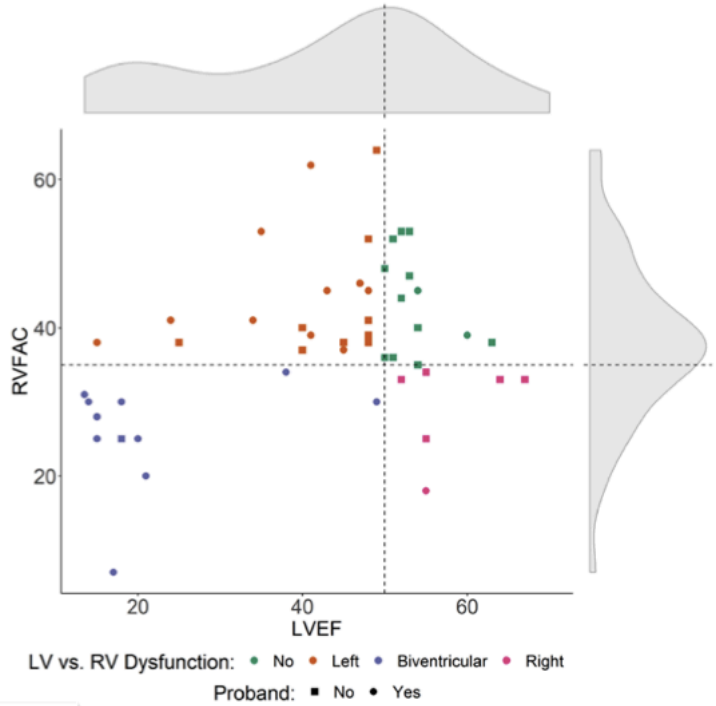
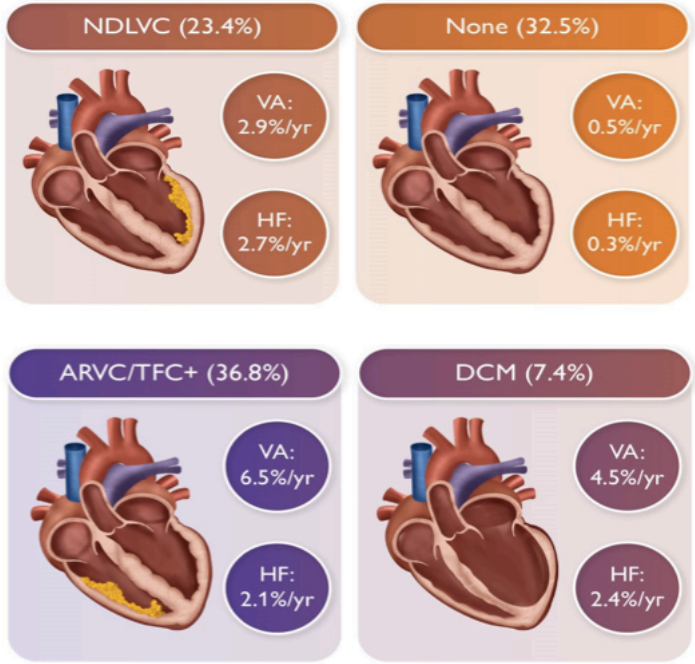
Genotype–phenotype correlations

FLNC



Gigli et al. *Circulation*. 2021;144:1600–1611

DSP



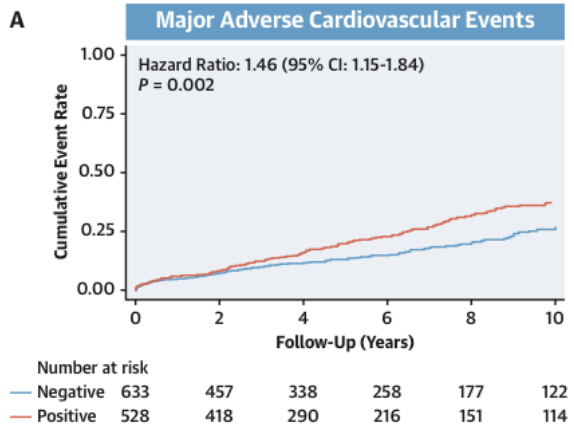
Gasperetti et al. European Heart Journal (202

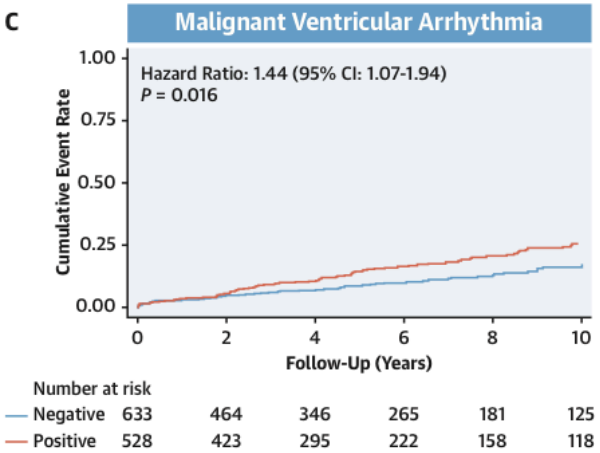
European Reference Networks

Prognosis (and therapy)

Worse Outcomes in Genotype-Positive DCM

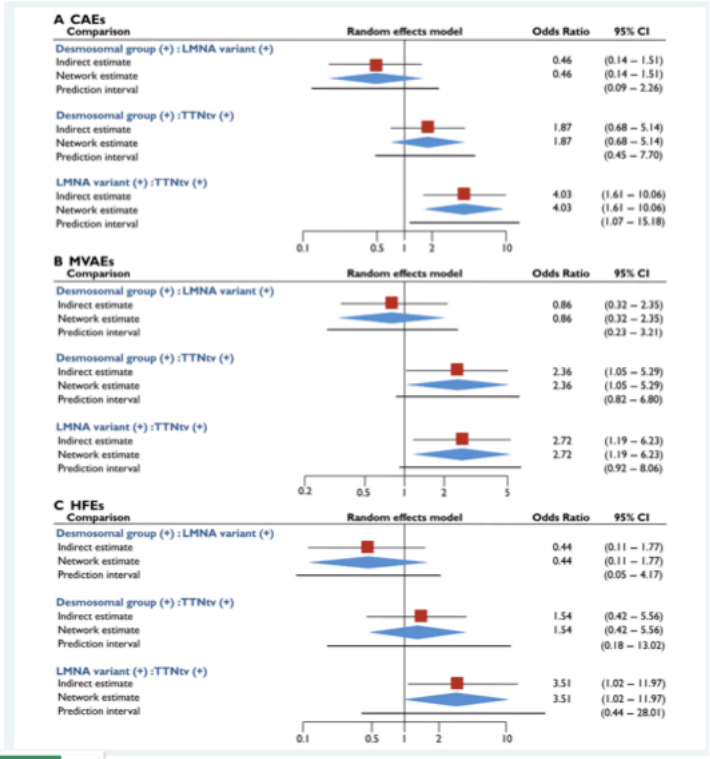
- **Major Adverse Cardiovascular Events**
  HR 1.51 (95% CI, 1.17-1.94; P = 0.001)
- **End-Stage Heart Failure**
  HR 1.67 (95% CI, 1.16-2.41; P = 0.006)
- **Malignant Ventricular Arrhythmia**
  HR 1.50 (95% CI, 1.09-2.07; P = 0.013)
- **Left Ventricular Reverse Remodeling**
  OR 0.77 (95% CI, 0.59-0.99; P = 0.047)





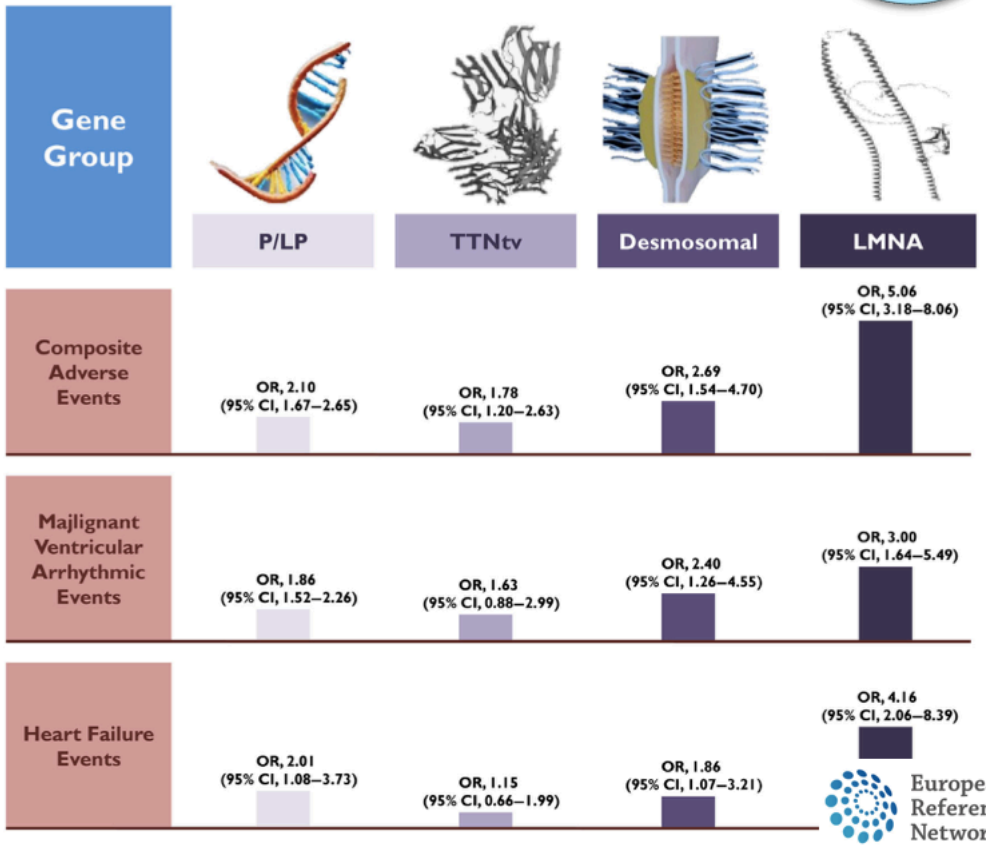
Escobar-Lopez, L. et al. J Am Coll Cardiol. 2021;78(17):1682-1699.

Prognostic implications of genotype findings in non-ischaemic dilated cardiomyopathy: A network meta-analysis



26 studies
- 1,382 genotype positive (P/LP) patients
- 645 truncating titin (TTNtv) patients
- 62 desmosomal gene patients
- 119 lamin A/C (LMNA) patients
- No difference in LVEF between gene groups

Prognosis



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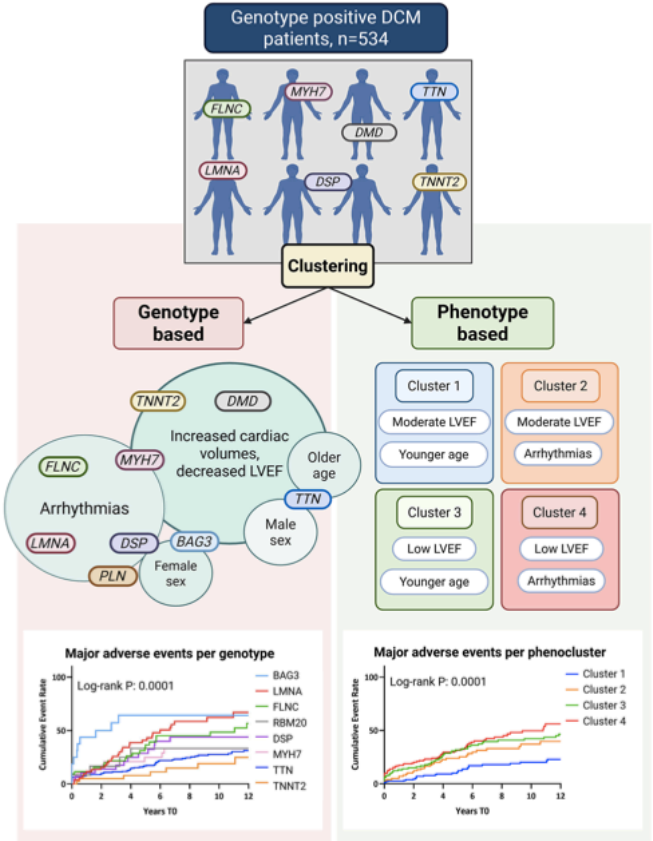
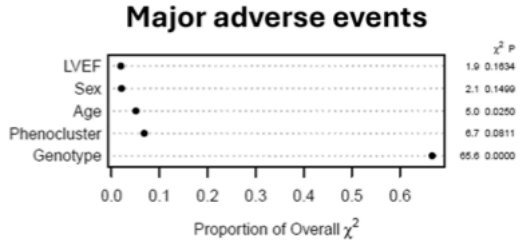
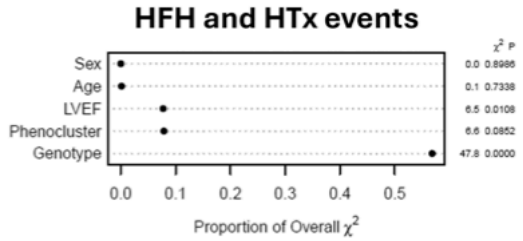
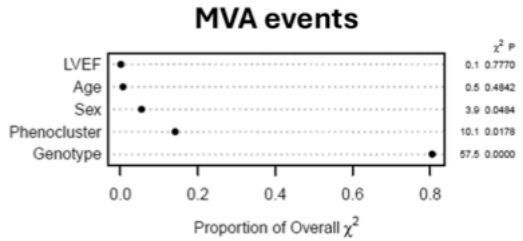
Anastasiou et al. European Journal of Heart Failure (2024) 26, 2155–2168

Impact of genotype–phenotype associations on prognosis in dilated cardiomyopathy









Stroeks et al. European Journal of Heart Failure 2025

JAMA | Original Investigation

Risk Stratification in Nonischemic Dilated Cardiomyopathy Using CMR Imaging

A Systematic Review and Meta-Analysis

...the weakness of LVEF

Figure 1. Cardiac Magnetic Resonance (CMR) Imaging Parameters and Clinical Outcomes

Parameter	Studies/ patients, No.	HR (95% CI)
Late gadolinium enhancement presence (yes/no)		
All-cause mortality	23/9738	1.81 (1.60-2.04)
Cardiovascular mortality	19/5228	2.43 (2.13-2.78)
Arrhythmia	40/13 791	2.69 (2.20-3.30)
Heart failure	32/9464	1.98 (1.73-2.27)
MACE	54/12 040	2.09 (1.79-2.44)
Late gadolinium enhancement extent (per 1%)		
All-cause mortality	4/1852	1.07 (1.02-1.12)
Cardiovascular mortality	3/1323	1.15 (1.07-1.24)
Arrhythmia	9/2086	1.07 (1.03-1.12)
Heart failure	6/1686	1.06 (1.01-1.10)
MACE	13/3004	1.03 (1.02-1.04)
Left ventricular ejection fraction (per 1%)		
All-cause mortality	5/3220	0.99 (0.97-1.02)
Cardiovascular mortality	7/3522	0.97 (0.94-1.00)
Arrhythmia	12/5055	0.99 (0.97-1.01)
Heart failure	10/4576	0.97 (0.95-0.98)
MACE	24/5446	0.98 (0.96-0.99)
T1 relaxation time (per 10 ms)		
Arrhythmia	5/1778	1.07 (1.01-1.14)
Heart failure	3/2198	1.03 (0.93-1.13)
MACE	3/962	1.06 (1.01-1.11)
Extracellular volume (per 1%)		
Heart failure	3/1372	1.09 (0.91-1.30)
Global longitudinal strain (per 1%)		
Heart failure	3/1001	1.06 (0.95-1.18)
MACE	7/1397	1.03 (0.94-1.14)

JAMA. doi:10.1001/jama.2024.13946
Published online September 19, 2024.

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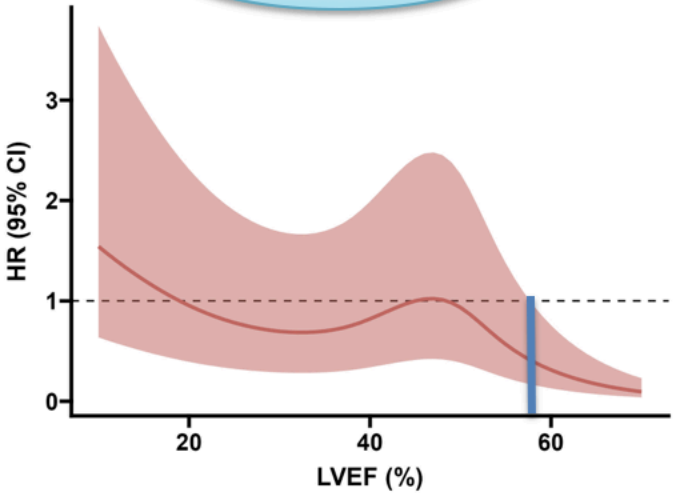
Stratify the genotypes…the weakness of LVEF

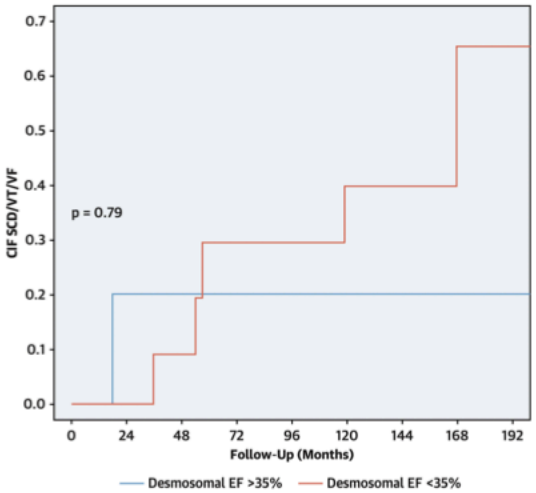
Prognosis

FLNC

DSP



The patient's genotype should be considered in the estimation of SCD risk in DCM.[185,186,869,886]	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 (see *Table 21*).[541,542,867,869,873,878,881,886]	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 (see *Table 21*).[869,873,881,886]	IIb	C



Gigli, Mestroni, Sinagra et al. JAMA Cardiology 2025

Gigli, Mestroni, Sinagra et al. JACC 2019

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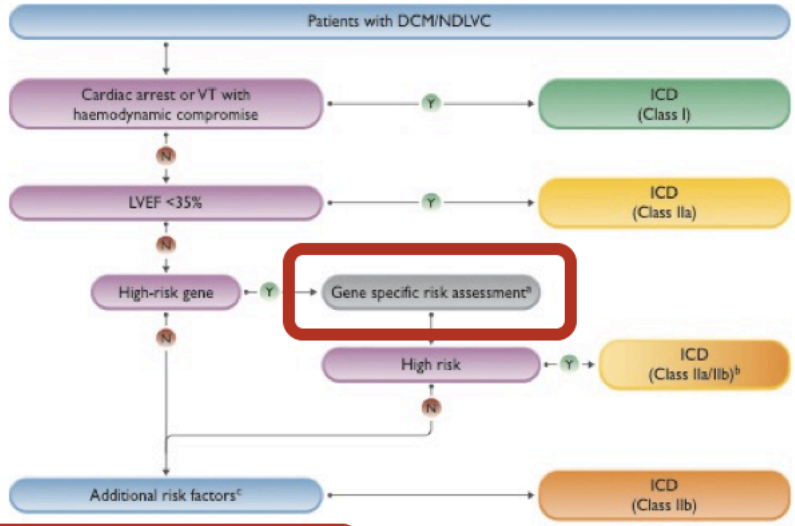
2023 CMP guidelines

Prognosis



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An ICD may be considered in selected patients with DCM with a genotype associated with high SCD risk % without additional risk factors (see [3,881,886	IIb	C

Gene	Annual SCD rate	Predictors of SCD
LMNA[185,186,438,541,865,878,879]	5–10%	Estimated 5-year risk of life-threatening arrhythmia using *LMNA* risk score (https://lmna-risk-vta.fr)
FLNC-truncating variants[866,867,880]	5–10%	LGE on CMR LVEF < 45%
TMEM43[868,881]	5–10%	Male Female and any of the following: LVEF <45%, NSVT, LGE on CMR, >200 VE on 24h Holter ECG
PLN[542,882,883]	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[185,186]	3–5%	LGE on CMR LVEF < 45%
RBM20[869]	3–5%	LG LVI

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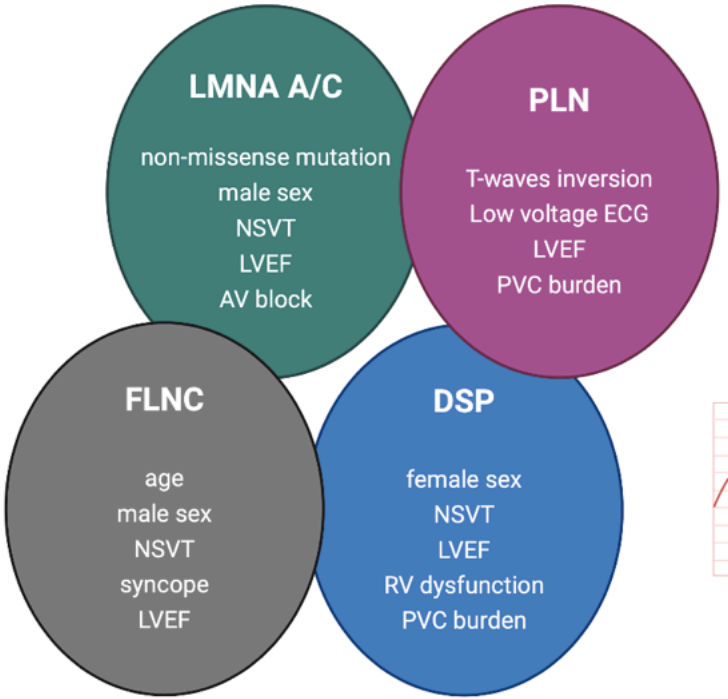
Gene-specific personalized risk estimation

Prognosis



- https://www.dsp-risk.com/
- https://flnctv.shinyapps.io/RiskCalculator/
- http://lmna-risk-vta.fr/
- https://plnriskcalculator.shinyapps.io/final_shiny/

Gigli M, Sinagra G, et al. European Journal of Heart Failure 2025 – HFA consensus

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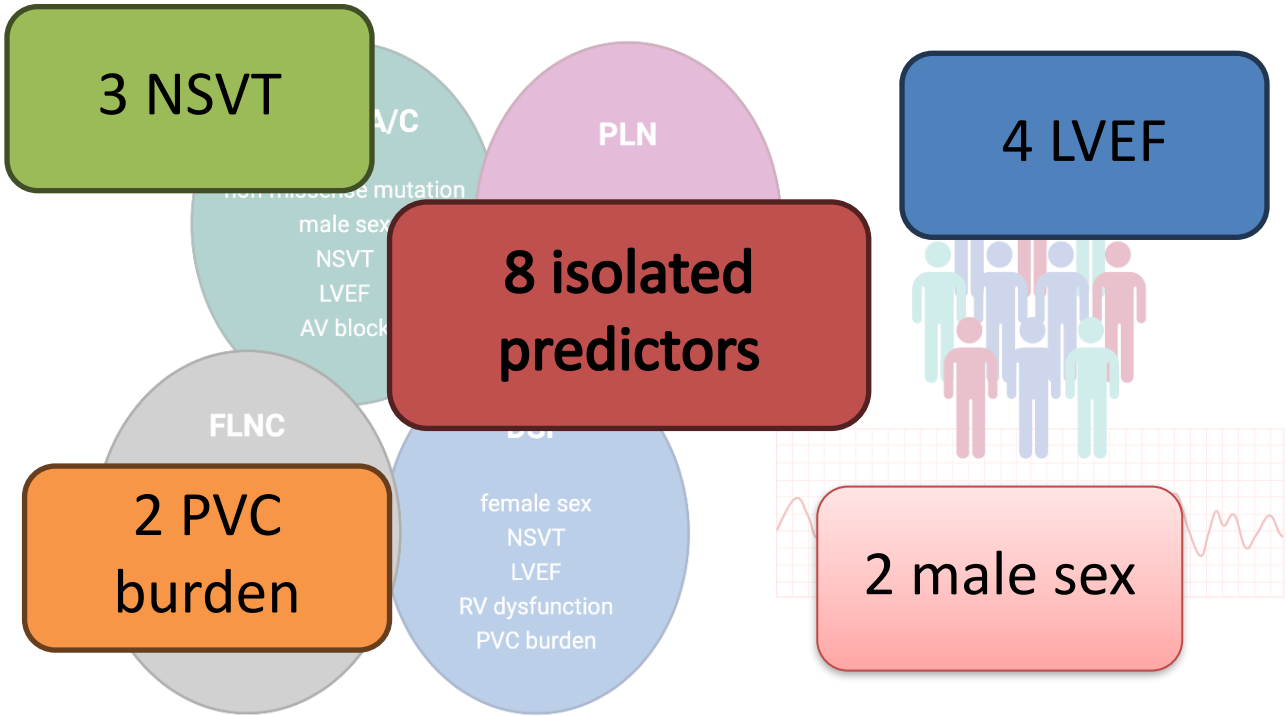
Gene-specific risk scores in DCM/NDLVC

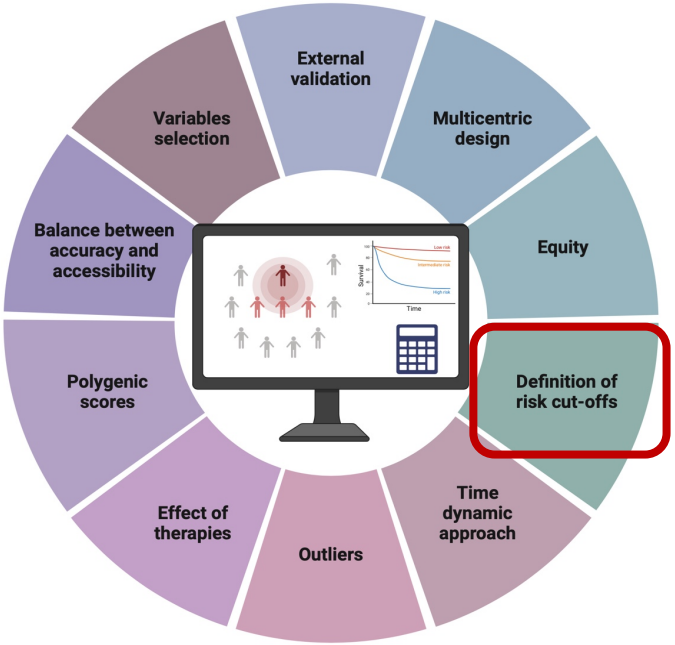
Prognosis

Gene-specific personalized risk estimation



Gigli M, Sinagra G, et al. European Journal of Heart Failure 2025 – HFA consensus

What is the reasonable threshold for ICD implantation?



…the Task Force acknowledges the **challenges associated with defining universal thresholds** for acceptable risk across different cardiomyopathy phenotypes, but is of the opinion that a **similar approach to** that taken in risk stratification for **HCM** is reasonable. **Although the *2022 ESC Guidelines*** *for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death* have suggested a higher **threshold of 10%** risk at 5 years to guide primary prevention ICD implantation in patients with **DCM and *LMNA* variants**

ESC 2023 cardiomyopathies guidelines

ESC European Society of Cardiology
European Heart Journal (2025) **00**, 1–13
https://doi.org/10.1093/eurheartj/ehaf477

Major arrhythmias in non-dilated left ventricular cardiomyopathy: a novel prediction score

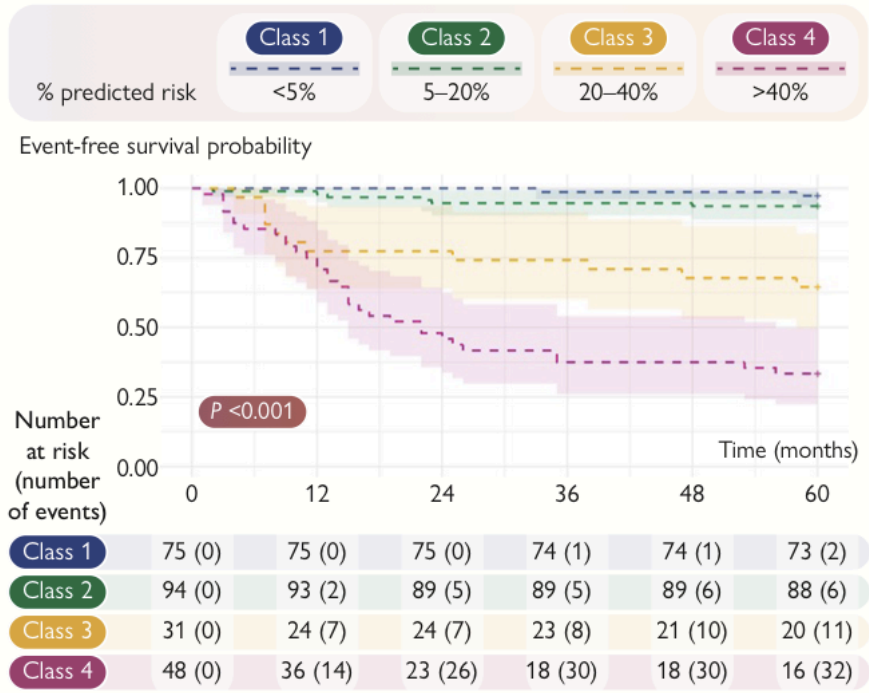
Prognosis

NDLVC-5y risk score for the prediction of 5-year MAE risk

Male sex	X 0.8605	
	+	
LVEF <45%	X 1.6967	
	+	
NSVT	X 1.1288	
	+	
Septal LGE	X 0.6929	
	+	
RLP LGE	X 0.2275	
	+	
PVs/LPVs HR	X 1.5336	
	+	
M-Infl	X 2.7535	
		PI

5-year risk of MAE:

$1 - (0.99600731958437)^{\exp(PI)}$



Peretto et al. European Heart Journal 2025

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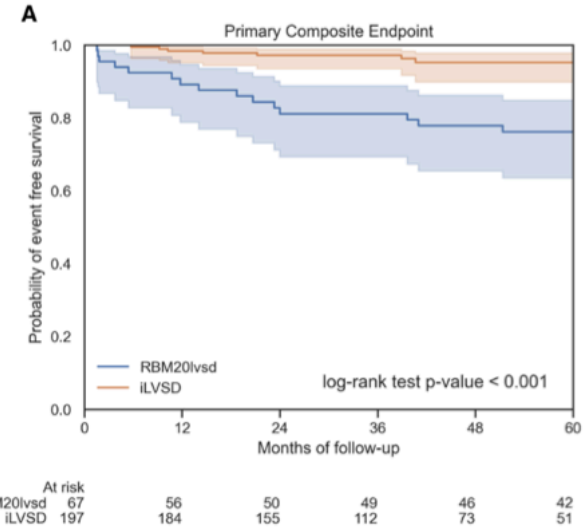
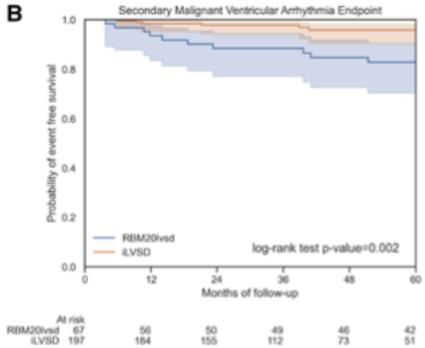
Arrhythmogenic genotypes – less frequent but not less dangerous

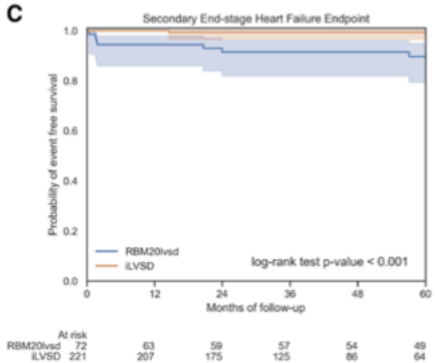
ORIGINAL ARTICLE

Risks of Ventricular Arrhythmia and Heart Failure in Carriers of RBM20 Variants

RBM20





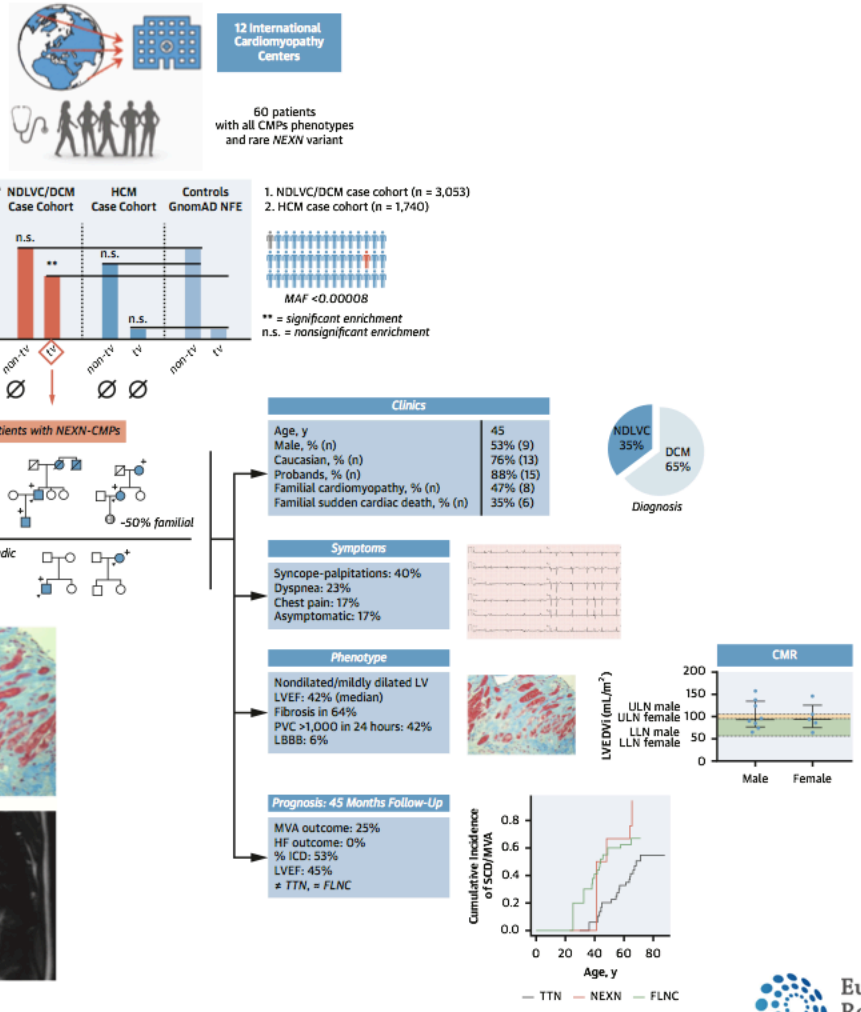


- 6-fold higher risk of composite outcome
- 40% MVA had EF>35%
- Similar risk of MVA in males vs females
- Higher risk of ESHF in males vs females

Cannie D et al. *Circ Genom Precis Med.* 2023;16:e004059

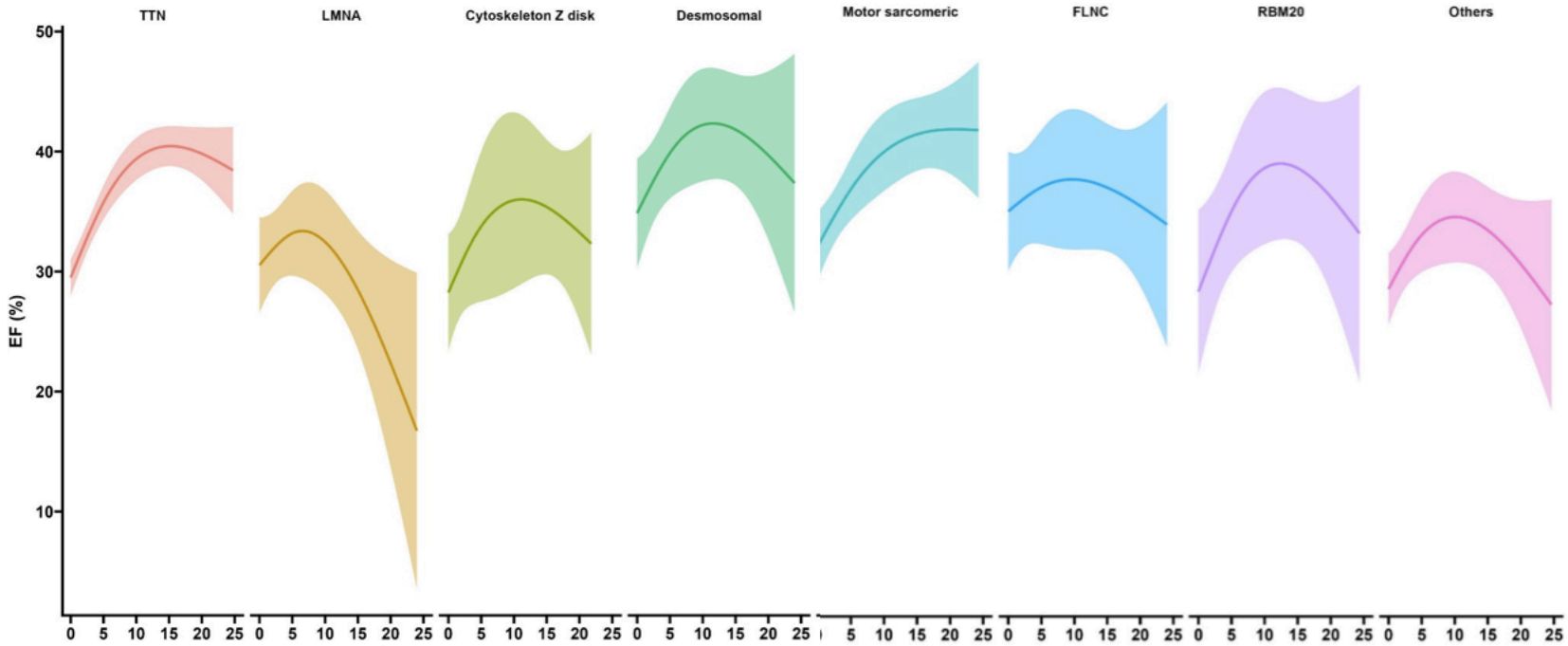
Genetic and Phenotypic Characterization of Nexilin (*NEXN*)–Related Cardiomyopathy

Results From a Multicentric Study



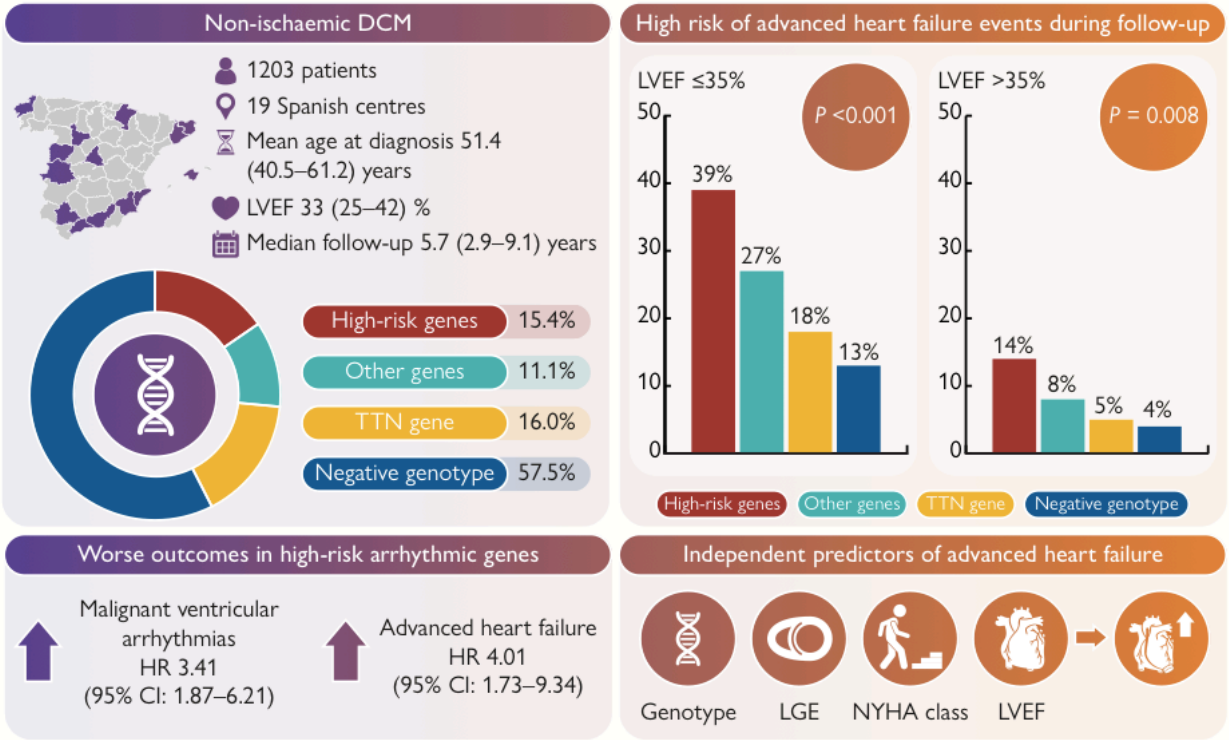
Perotto M, et al. JACC Heart Fail. 2025;13(9):102529.

Gene-specific LVEF trajectory



Manca P, Stolfo D, Gigli M, et al. unpublished

Arrhythmic genotypes in dilated cardiomyopathy and risk of advanced heart failure



Mora-Ayestarán et al. European Heart Journal 2025

ESC European Heart Journal (2026) 00, 1–14
https://doi.org/10.1093/eurheartj/ehag104

Laminopathies: natural history and risk prediction of heart failure

LMNA risk score for prediction of 5-year risk of major heart failure events

Analysis of registry data

Exclusion of patients with LVEF <30% at baseline

Derivation cohort
OPALE: nationwide registry on laminopathies
470 patients

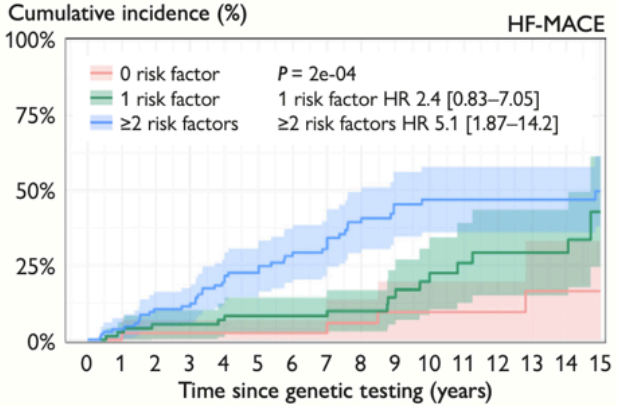
Validation cohort
Tertiary cardiology referral centres
245 patients

Five independent risk factors

	Adjusted HR
Male sex	1.86
LVEF <50%	2.18
Missense variants in head and rod domains	2.91
Complete left bundle branch block	2.99

Good discrimination of the model with C-index of 0.750 and 0.758 in the derivation and validation cohorts

An additive effect of risk factors



HF-MACE, heart failure-major adverse cardiac event; HR, hazard ratio; **LMNA**, lamin A/C gene; **LVEF**, left ventricular ejection fraction

Charron P, *et al. European Heart Journal.*

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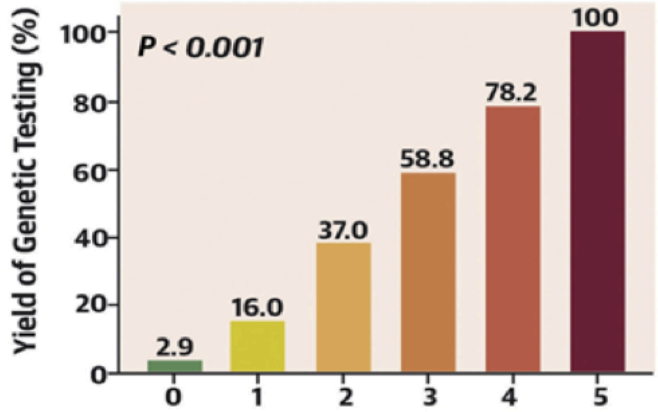
Genetic testing: a rationale approach

Clinical Risk Score to Predict Pathogenic Genotypes in Patients With Dilated Cardiomyopathy

Predictors of a Positive Genetic Result	
Clinical Predictors	**Points**
Skeletal myopathy	1
Family history of DCM	1
Low voltage on ECG	1
Absence of hypertension	1
Absence of LBBB	1
Scoring Range: 0 to 5 Points	

Yield of Positive Genotype According to the Score Category (n = 1,015)



ESC European Society of Cardiology
European Journal of Heart Failure (2026) 00, 1–9
https://doi.org/10.1093/ejhf/xuag055

RESEARCH ARTICLE

The yield and clinical impact of genetic testing in older patients with dilated cardiomyopathy

Douglas E. Cannie[1,2,*], Athanasios Bakalakos[1,2], Petros Syrris[1], Alexandros Protonotarios[1,2], Massimiliano Lorenzini[1,2], Oliver Guttmann[1,2], Constantinos O'Mahony[1,2], Konstantinos Savvatis[1,2,3], Neha Sekhri[2,3], Saidi Mohiddin[2,3], Luis R. Lopes[1,2], and Perry M. Elliott[1,2]

The Yield and Clinical Impact of Genetic Testing in Older Patients with Dilated Cardiomyopathy

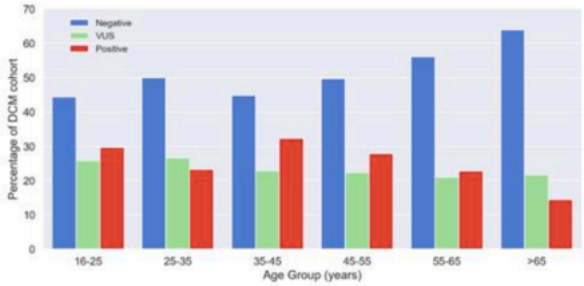
Single Centre DCM Cohort

686 patients with DCM undergoing genetic testing

62.1% male, age 50 (37, 59) years

24% with LP/P variants

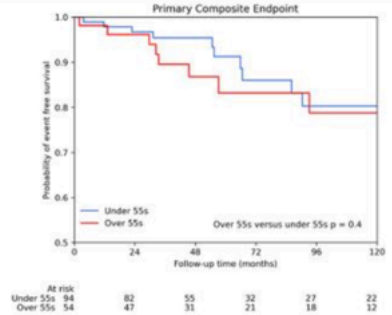
Yield of Genetic Testing by Age Group



One in five patients >55 years were genotype-positive.

30% of genotype-positive patients >55 years had high-risk genotypes.

Genotype-Positive Outcomes by Age

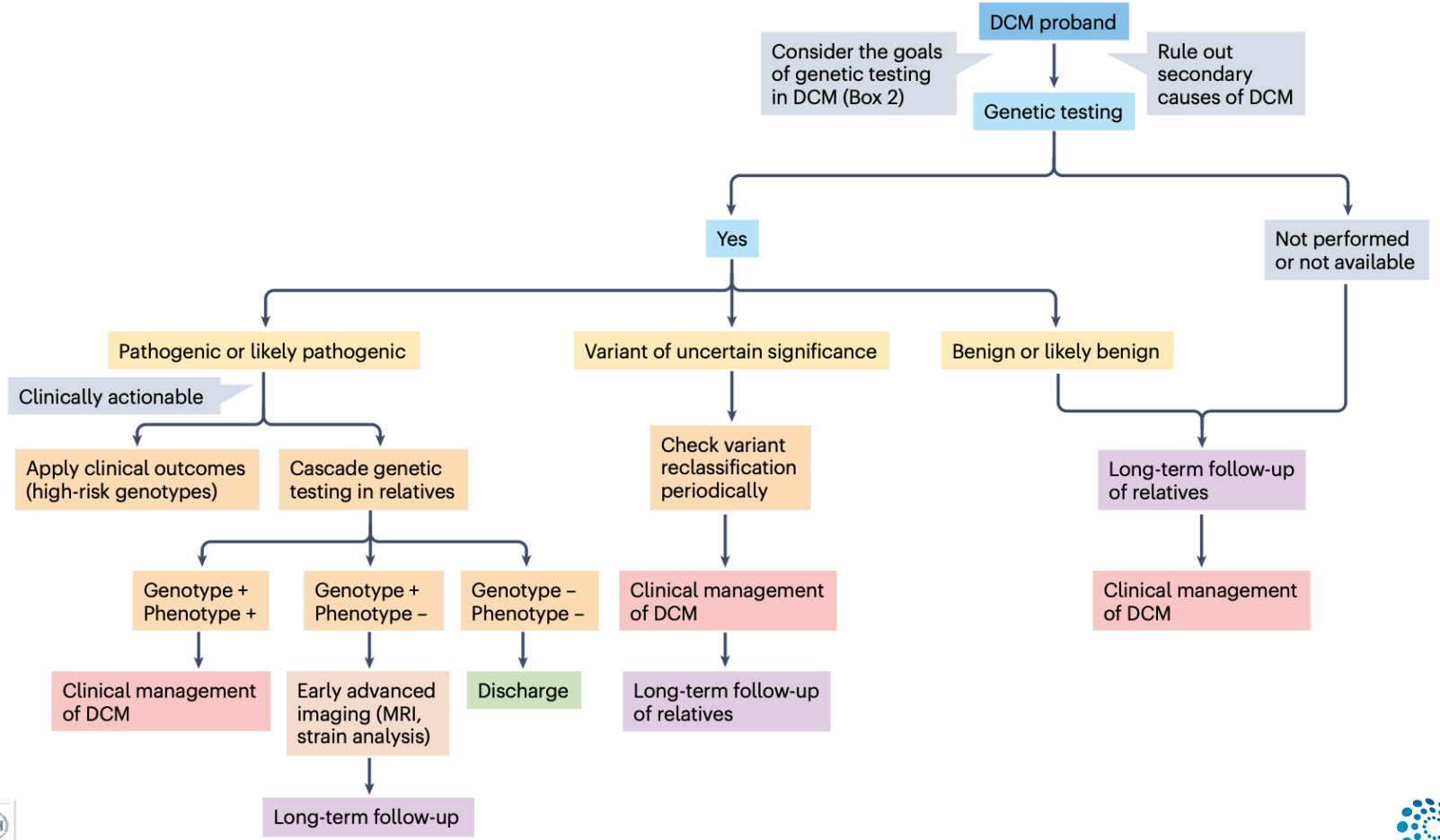


Age groups <55 vs >55 years

Similar risk of:

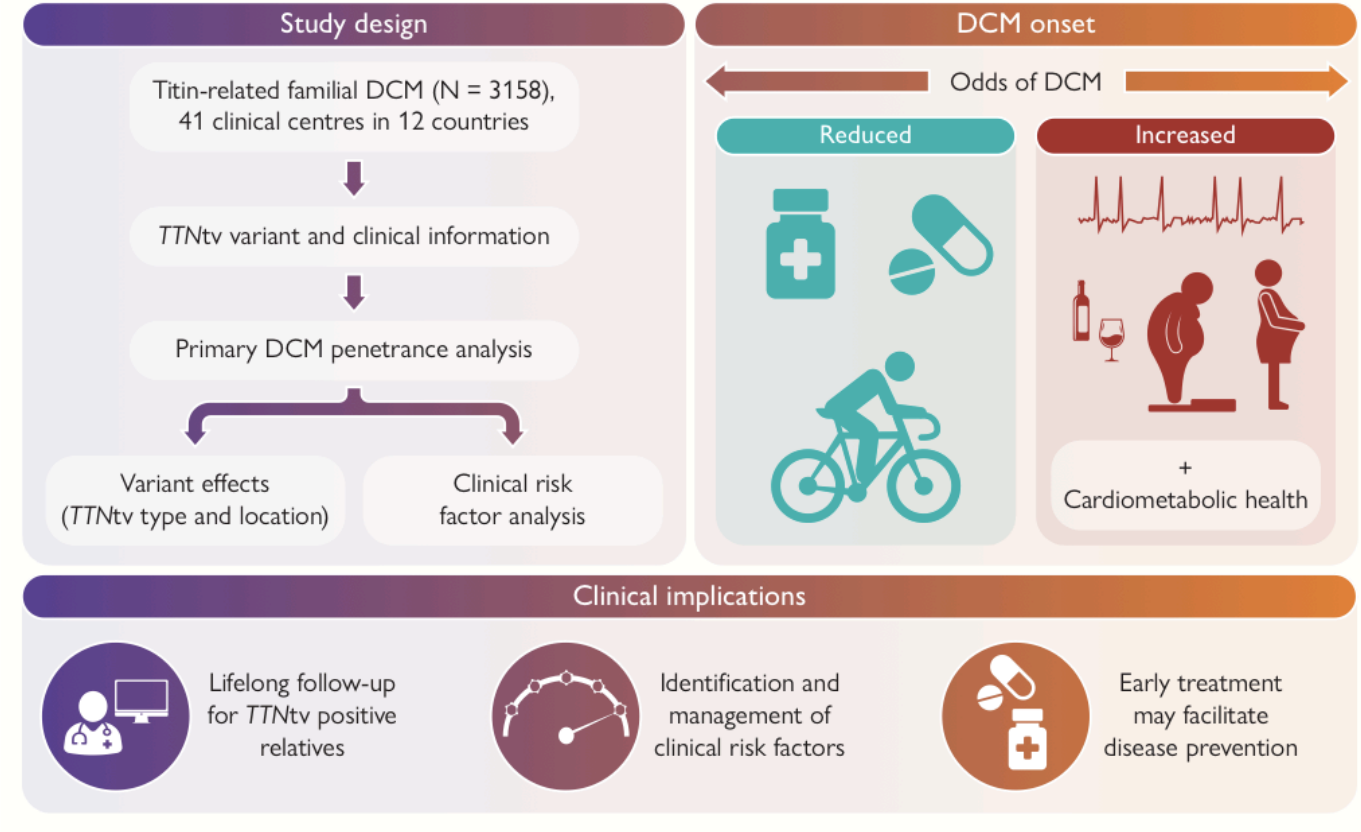
- Ventricular arrhythmia
- End-stage heart failure

Genetic testing: a rationale approach



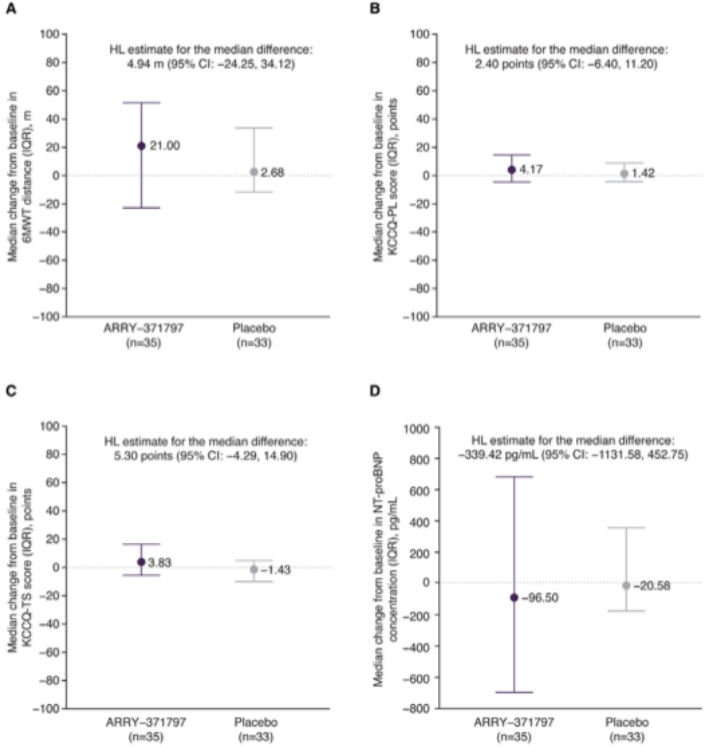
Nature reviews Card, Gigli, Sinagra, Mestroni et al. 2024

Titin-related familial dilated cardiomyopathy: factors associated with disease onset



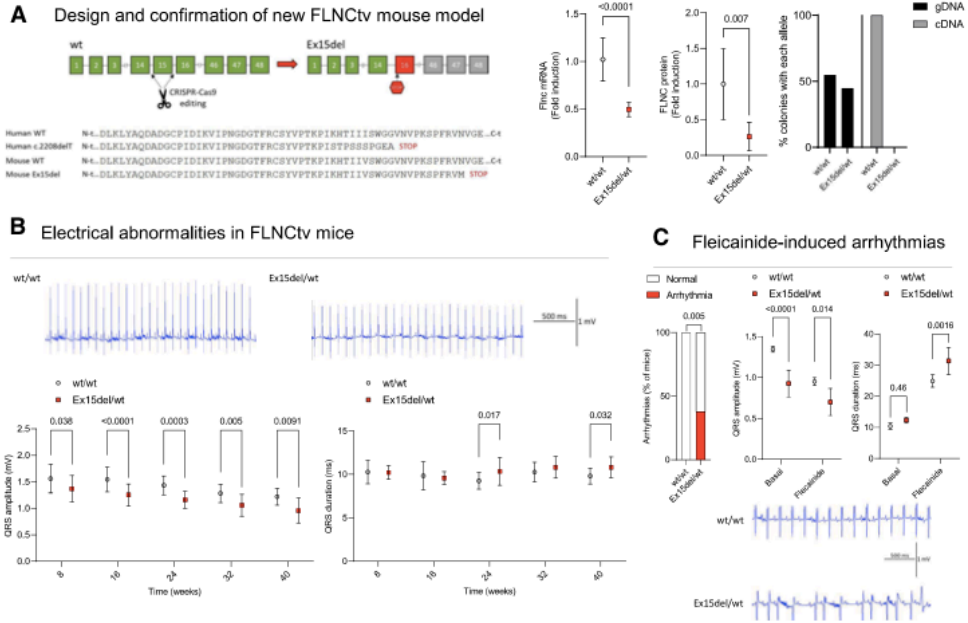
Fatkin D. et al. European Heart Journal (2025) 00, 1–18

REALM-DCM: A Phase 3, Multinational, Randomized, Placebo-Controlled Trial of ARRY-371797 in Patients With Symptomatic *LMNA*-Related Dilated Cardiomyopathy



Garcia-Pavia P et al. Circ Heart Fail. 2024;17:e011548

CRISPR activation to repair electrocardiogram abnormalities caused by a FLNC truncating variant in mice



Cañas-Alvaro et al

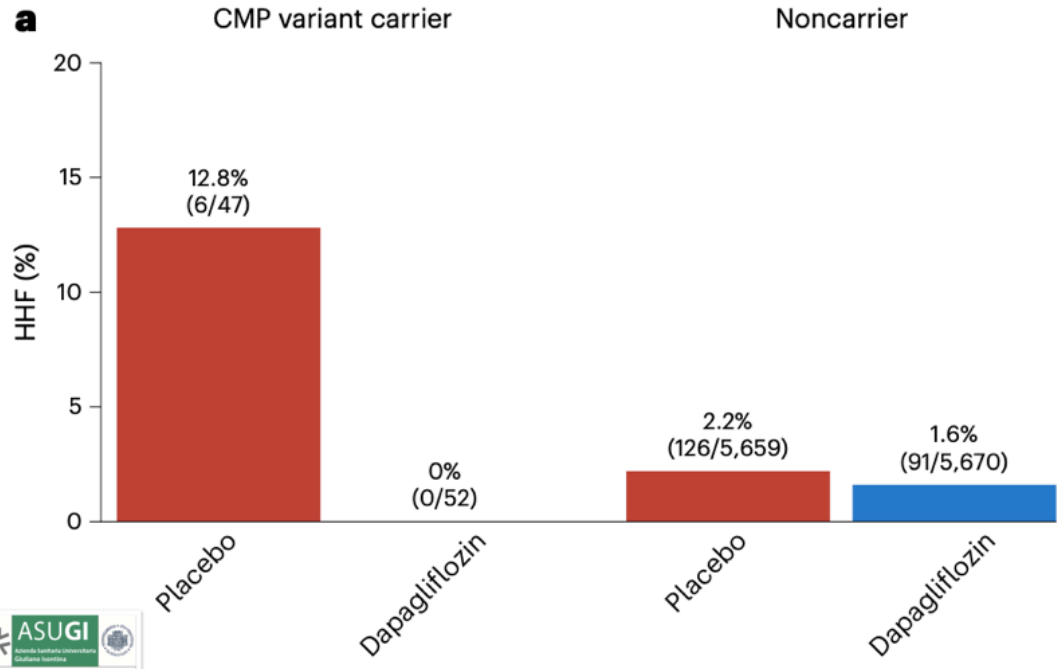
European Heart Journal (2025) **00**, 1–4

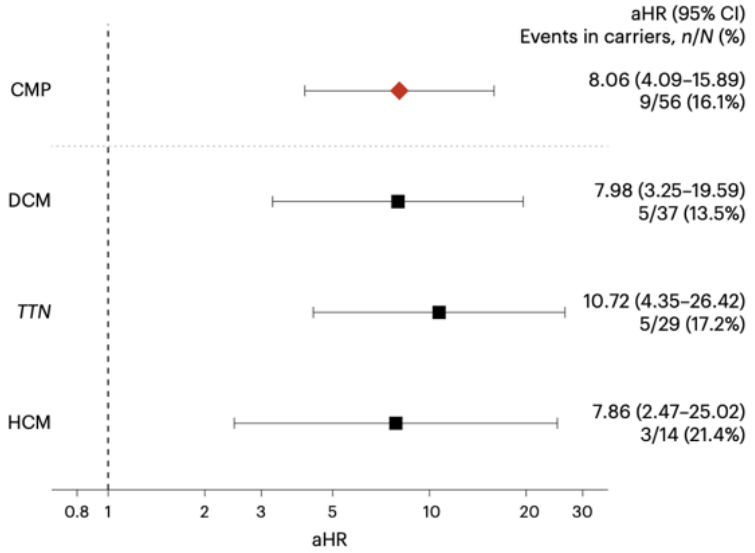
nature medicine

Article

https://doi.org/10.1038/s41591-026-04439-x

Effects of SGLT2 inhibition on incident heart failure in carriers of cardiomyopathy-associated genetic variants





Early Treatment With Candesartan vs Placebo in Genetic Carriers of Dilated Cardiomyopathy (EARLY-GENE Trial)

C Cristina Avendaño Solá

Status and phase

Enrolling | Phase 3

Conditions

Cardiomyopathy, Dilated

Treatments

Drug: Candesartan

Study type

Interventional

Funder types

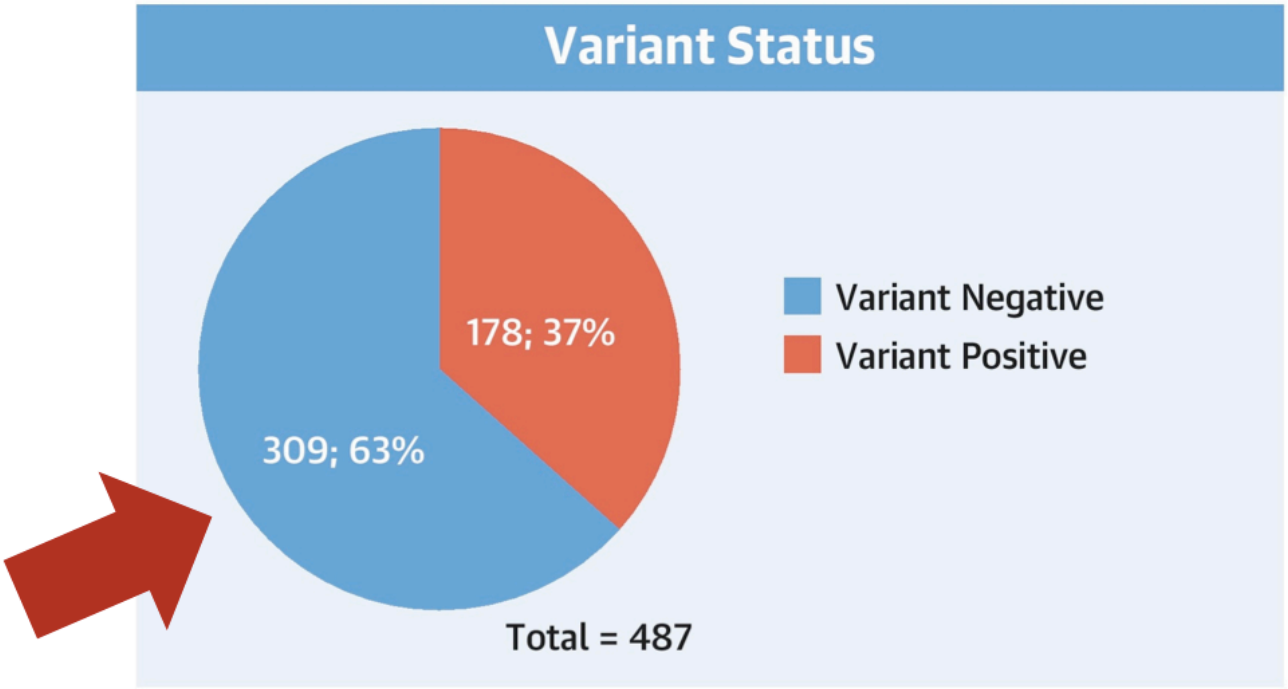
Other

Identifiers

NCT05321875

EARLY-GENE

But for gene elusive/not tested patients we still lack prognostic scores



Gigli, M. et al. J Am Coll Cardiol. 2019;74(11):1480-90.