

SCEGLIERE L'ICD: UNA SCELTA PERSONALIZZATA

Genetica e rischio aritmico nella cardiomiopatia non ischemica: quando cambia la decisione sull'ICD

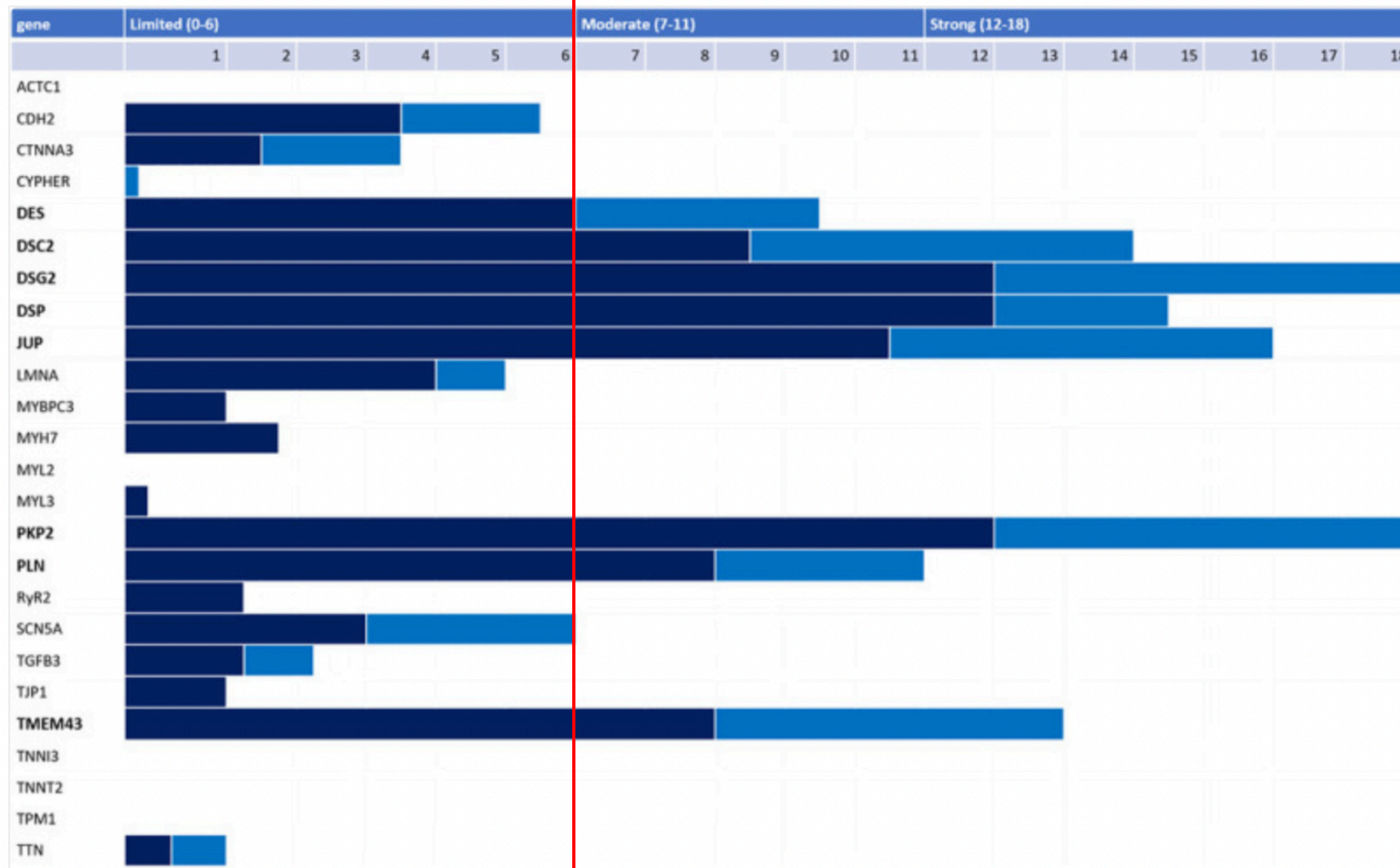
Paolo Cerea
ASST Valle Olona
Elettrofisiologia ed Elettrostimolazione



- Discussing ACM today no longer refers to a single disease, but to a spectrum of conditions that share a common hallmark — the progressive death of cardiomyocytes and their replacement by fibrofatty tissue, predisposing to the characteristic ventricular electrical instability.
- Numerous tools are available for risk stratification in ACM sub-populations, but it is essential to understand how the original populations were defined to avoid misapplying these tools to different groups.



ACM – GENOTYPE-BASED APPROACH

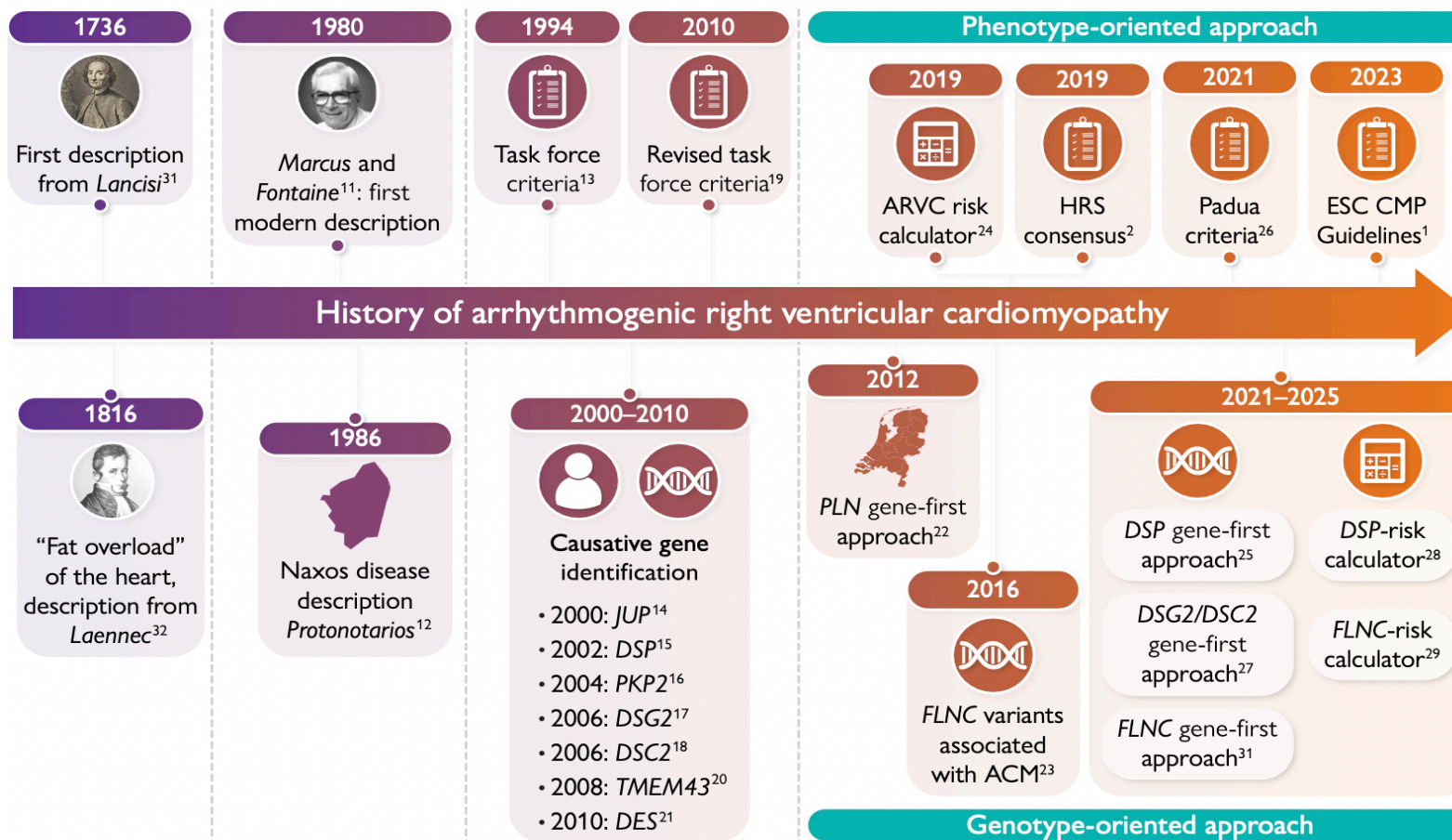


International Evidence Based Reappraisal of Genes Associated With Arrhythmogenic Right Ventricular Cardiomyopathy Using the Clinical Genome Resource Framework

Cynthia A. James¹, Jan D.H. Jongbloed², Ray E. Hersberger³, Ana Morales⁴, Daniel P. Judge⁵, Petros Syrris⁶, Kallioi Pilichou⁷, Argelia Medeiros Domingo⁸, Brittny Murray⁹, Julia Cadrin-Tourigny¹⁰, Ronald Lekanne Deprez¹⁰, Rudy Celeghin⁷, Alexandros Protonotarios⁶, Babken Asatryan⁶, Emily Brown¹, Elizabeth Jordan³, Jennifer McGlaughon¹¹, Courtney Thaxton¹¹, C. Lisa Kurtz¹¹, J. Peter van Tintelen^{10, 12}



ACM – GENE-BASED APPROACH



Arrhythmogenic right ventricular cardiomyopathy, *European Heart Journal*, 2026; ehag297; Gasperetti et al



DISEASE-LEVEL

ESC
European Society
of Cardiology

European Heart Journal (2022) 43, e1–e9
<https://doi.org/10.1093/eurheartj/ehac180>

CLINICAL RESEARCH
Arrhythmia/electrophysiology

A new prediction model for ventricular arrhythmias in arrhythmogenic right ventricular cardiomyopathy

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European Heart Journal (2022) 43, 3053–3067
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CLINICAL RESEARCH
Heart failure and cardiomyopathies

Importance of genotype for risk stratification in arrhythmogenic right ventricular cardiomyopathy using the 2019 ARVC risk calculator

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CLINICAL RESEARCH
Heart failure and cardiomyopathies

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

GENE-LEVEL

A novel tool for arrhythmic risk stratification in desmoplakin gene variant carriers

Richard T Carrick¹, Alessio Gasperetti^{1 2 3}, Alexandros Protonotarios⁴, Brittney Murray¹, Mikael Laredo⁵, Iris van der Schaaf³, Dennis Dooijes³, Petros Syrris⁴, Douglas Cannie⁴, Crystal Tichnell¹, Nisha A Gilotra¹, Chiara Cappelletto⁶, Kristen Medo⁷, Ardan M Saguner⁸, Firat Duru⁸, Robyn J Hyland⁹, Dominic J Abrams⁹, Neal K Lakdawala¹⁰, Julia Cadrin-Tourigny¹¹, Mattia Targetti¹², Iacopo Olivetto¹², Maddalena Graziosi¹³, Moniek Cox¹⁴, Elena Biagini¹³, Philippe Charron⁵, Paolo Compagnucci¹⁵, Michela Casella^{15 16}, Giulio Conte¹⁷, Claudio Tondo^{18 19}, Momina Yazdani^{20 21}, James S Ware^{20 21}, Sanjay K Prasad^{20 21}, Leonardo Calò²², Eric D Smith²³, Adam S Helms²³, Sophie Hespe²⁴, Jodie Ingles²⁴, Harikrishna Tandri¹, Flavie Ader^{25 26}, Giovanni Peretto²⁷, Stacey Peters²⁸, Ari Horton²⁸, Jessica Yao²⁸, Eric Schulze-Bahr²⁹, Sven Dittman²⁹, Eric D Carruth³⁰, Katelyn Young³⁰, Maria Qureshi³⁰, Chris Haggerty^{30 31}, Victoria N Parikh³², Matthew Taylor⁷, Luisa Mestroni⁷, Arthur Wilde^{33 34}, Gianfranco Sinagra⁶, Marco Merlo⁶, Estelle Gandjbakhch⁵, J Peter van Tintelen^{2 35}, Anneline S J M Te Riele^{3 35}, Perry Elliott⁴, Hugh Calkins¹, Katherine C Wu¹, Cynthia A James¹

Development and Validation of a New Risk Prediction Score for Life-Threatening Ventricular Tachyarrhythmias in Laminopathies

Karim Wahbi, MD, PhD[✉], Rabah Ben Yaou, MD, Estelle Gandjbakhch, MD, PhD, Frédéric Anselme, MD, PhD, Thomas Gossios, MD, Neal K. Lakdawala, MD, PhD, Caroline Stalens, PhD, ... [SHOW ALL](#) ... , and Denis Duboc, MD, PhD | [AUTHOR INFO & AFFILIATIONS](#)

MUTATIONAL-LEVEL

Prediction of ventricular arrhythmia in phospholamban p.Arg14del mutation carriers—reaching the frontiers of individual risk prediction

Tom E Verstraelen¹, Freyja H M van Lint^{2 3}, Laurens P Bosman⁴, Remco de Brouwer⁵, Virginnio M Proost¹, Bob G S Abeln¹, Karim Taha⁴, Aeilko H Zwinderman⁶, Cathelijne Dickhoff⁷, Toon Oomen⁸, Bas A Schoonderwoerd⁹, Gerardus P Kimman¹⁰, Arjan C Houweling², Juan R Gimeno-Blanes^{11 12}, Folkert W Asselbergs^{4 13}, Paul A van der Zwaag¹⁴, Rudolf A de Boer⁵, Maarten P van den Berg⁵, J Peter van Tintelen^{2 3}, Arthur A M Wilde^{1 12}

Features of the electrocardiogram in *TMEM43* p.S358L arrhythmogenic cardiomyopathy ^②

Stephen A. Duffett, MD,¹ Chris Compton, MSc,¹ Kieran Vasanathan, MD,¹ Ian Short, MD,¹ Harinder Pal Gill, MD,¹ Terry-Lynn Young, PhD,² Sean P. Connors, MD, DPhil,¹ Kathleen A. Hodgkinson, PhD^{2,3}

Prof. P. Van Tintelen
Genotype-Phenotype correlation in ACM



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Recommendation Table 29 — Recommendations for sudden cardiac death prevention in patients with arrhythmogenic right ventricular cardiomyopathy

Recommendations	Class ^a	Level ^b
Secondary prevention		
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with ARVC who have survived a cardiac arrest or have recovered from a ventricular arrhythmia causing haemodynamic instability. ^{939,943,944,948,949}	I	A
An ICD should be considered in ARVC patients who have suffered a haemodynamically tolerated VT. ^{522,939,943–945,948–950}	Ila	B
Primary prevention		
High-risk features ^c should be considered to aid individualized decision-making for ICD implantation in patients with ARVC. ^{538,939}	Ila	B
The updated 2019 ARVC risk calculator should be considered to aid individualized decision-making for ICD implantation in patients with ARVC. ^{d,524,526,536–539}	Ila	B

^cHigh-risk features: arrhythmic syncope, NSVT, RVEF <40%, LVEF <45%, SMVT at PES.

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Table 21 High-risk genotypes and associated predictors of sudden cardiac death

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

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Primary prevention

An ICD should be considered to reduce the risk of sudden death and all-cause mortality in patients with NDLVC, heart failure symptoms, and LVEF ≤35% despite >3 months of OMT.^{861,885}

Ila **A**

The patient's genotype should be considered in the estimation of SCD risk in NDLVC.

Ila **C**

An ICD should be considered in patients with NDLVC with a genotype associated with high SCD risk and LVEF >35% in the presence of additional risk factors (see [Table 21](#)).^{185,186,438,541,542,865–869,878–883}

Ila **C**

An ICD may be considered in selected patients with NDLVC with a genotype associated with high SCD risk and LVEF >35% without additional risk factors (see [Table 21](#)).

Ilb **C**

An ICD may be considered in patients with NDLVC without a genotype associated with high SCD risk and LVEF >35% in the presence of additional risk factors.^c

Ilb **C**

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Circulation: Arrhythmia and Electrophysiology

ORIGINAL ARTICLE



Sudden Cardiac Death Prediction in Arrhythmogenic Right Ventricular Cardiomyopathy

A Multinational Collaboration

RESEARCH ARTICLE

Originally Published 7 October 2022 |  |    

 Check for updates

Programmed Ventricular Stimulation as an Additional Primary Prevention Risk Stratification Tool in Arrhythmogenic Right Ventricular Cardiomyopathy: A Multinational Study

Primary prevention

High-risk features^c should be considered to aid individualized decision-making for ICD implantation in patients with ARVC.^{538,939}

The updated 2019 ARVC risk calculator should be considered to aid individualized decision-making for ICD implantation in patients with ARVC.^{d,524,526,536–539}

IIa

B

IIa

B

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ORIGINAL ARTICLE



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RESEARCH ARTICLE | Originally Published 7 October 2022 |  |  |  |  | 

 Check for updates

**Programmed Ventricular Stimulation as an
Additional Primary Prevention Risk
Stratification Tool in Arrhythmogenic Right
Ventricular Cardiomyopathy: A
Multinational Study**

SUSTAINED VA MODEL

FAST VT/VF/SCA MODEL

PVS ADJUSTED MODEL

OPTIONAL: programmed ventricular stimulation (PVS)

☒ N/A ☐ Positive ☐ Negative

Positive if induction of sustained monomorphic VT lasting >30s or with hemodynamic compromise



Age at diagnosis

Age at which the patient fulfilled ARVC diagnosis as per 2010 Task Force Criteria (Marcus et al. 2010)

Sex

☐ Male

☐ Female

Cardiac syncope (<6 months)

☐ Yes

☐ No

Syncope suspected to be caused by cardiac arrhythmia within 6 months prior to diagnosis.

Number of inverted T-waves

0

Total number of precordial and inferior leads with inverted T-waves on standard 12-lead ECG.

Maximum 24 hours PVC count

Maximum number of PVCs in 24 hours registered by continuous ECG monitoring (e.g. Holter)

History of non-sustained VT

☐ Yes

☐ No

Specified as a recorded ventricular tachycardia (>100bpm) ending spontaneously within 30 seconds.

Right ventricular ejection fraction (%)

50

As measured by cardiac MRI.

<https://arvcrisk.com/>

Risk of first sustained VA (any type), within:

☒ 5 years ☐ 2 years ☐ 1 year

Adjusted by PVS result (if available):

Calculate

ALL PATIENTS WITH DEFINITE ARVC

I.e. regardless of prior sustained VA

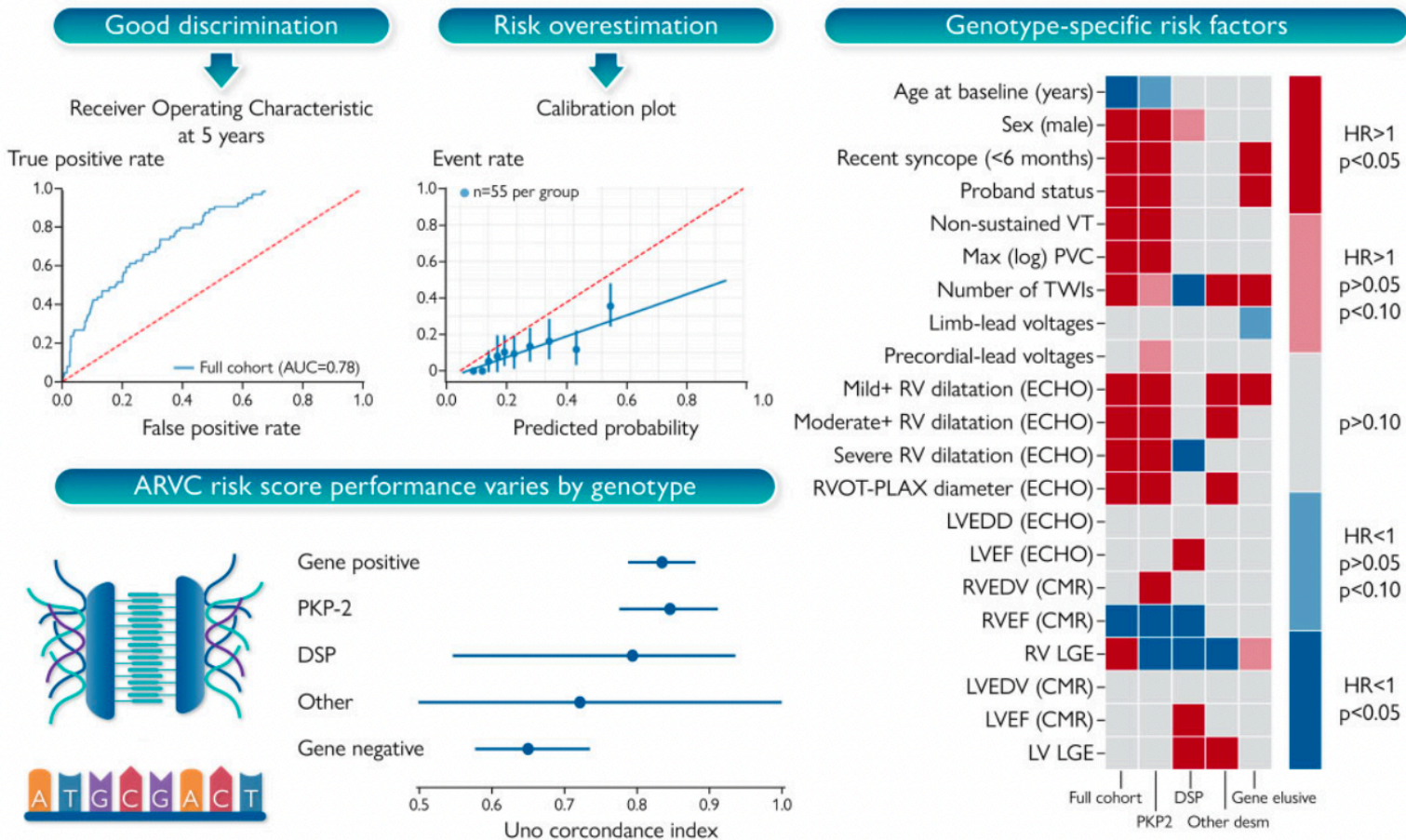
Risk of fast VT(>250bpm)/VF/SCA, within:

☒ 5 years ☐ 2 years ☐ 1 year

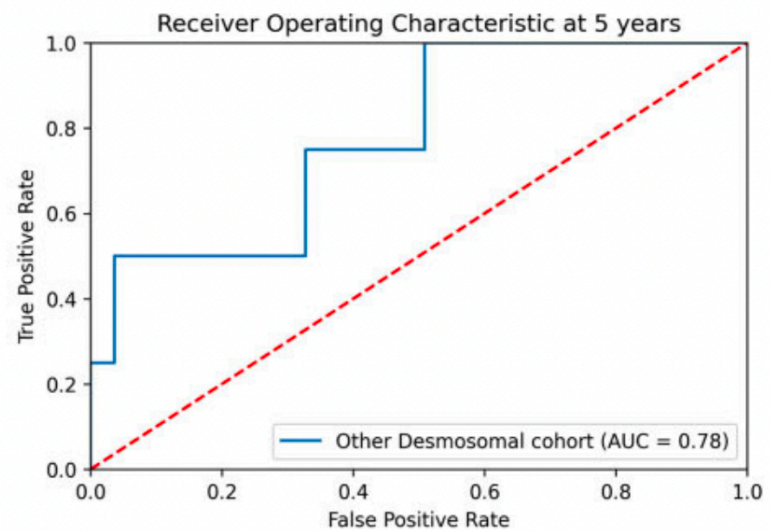
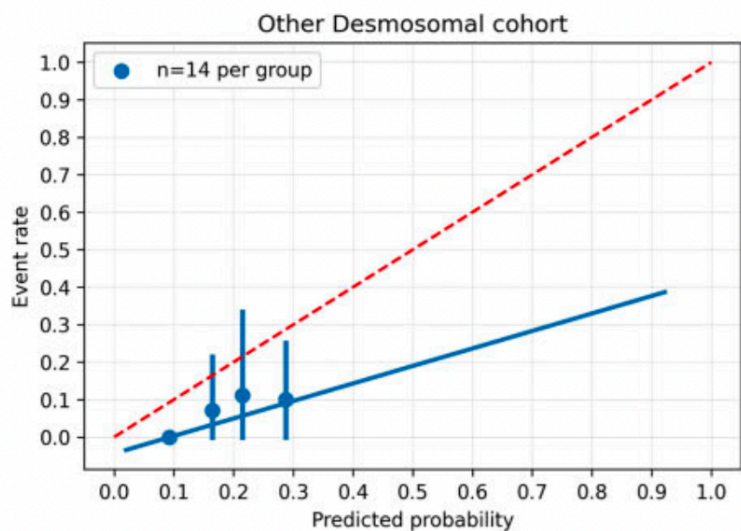
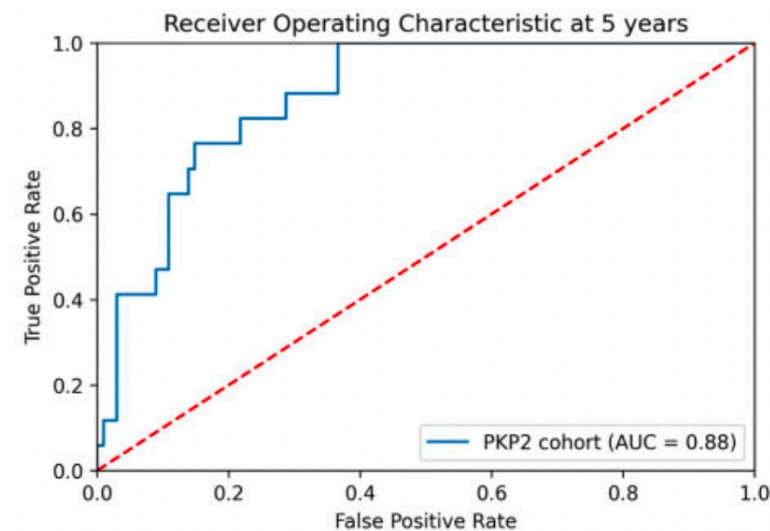
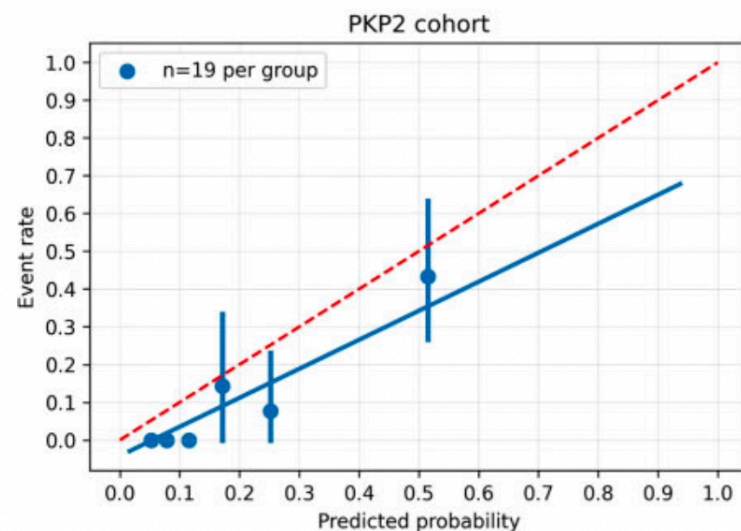
Calculate



Importance of genotype for risk stratification in arrhythmogenic right ventricular cardiomyopathy using the 2019 ARVC risk calculator



DISEASE LEVEL?

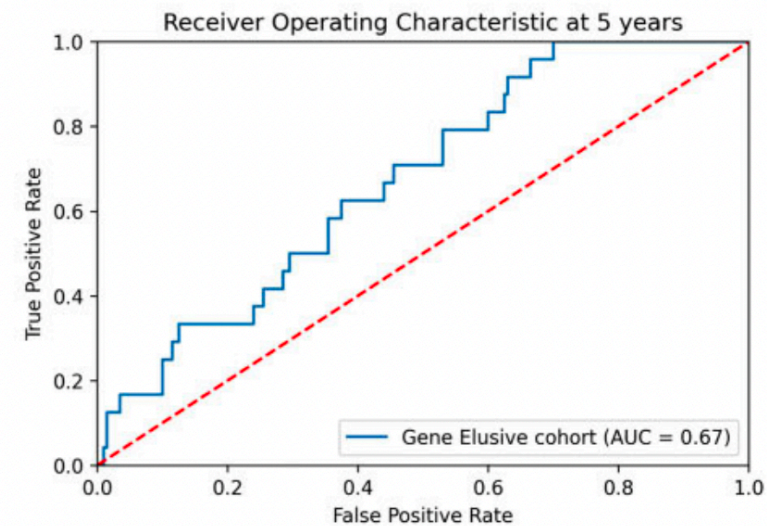
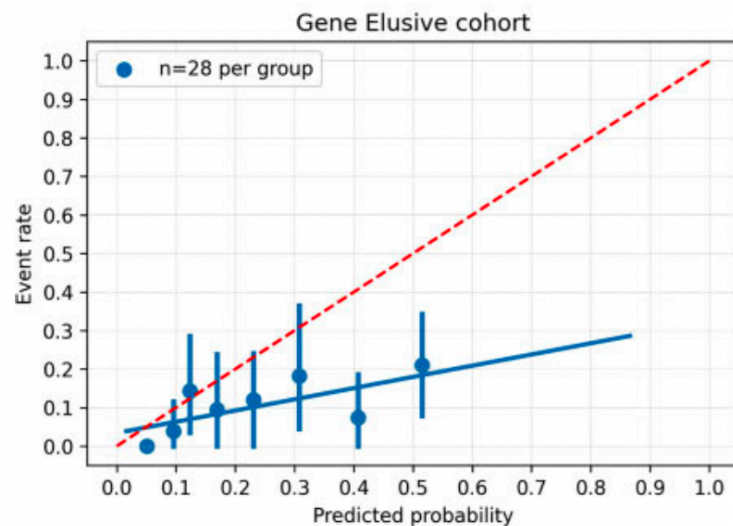
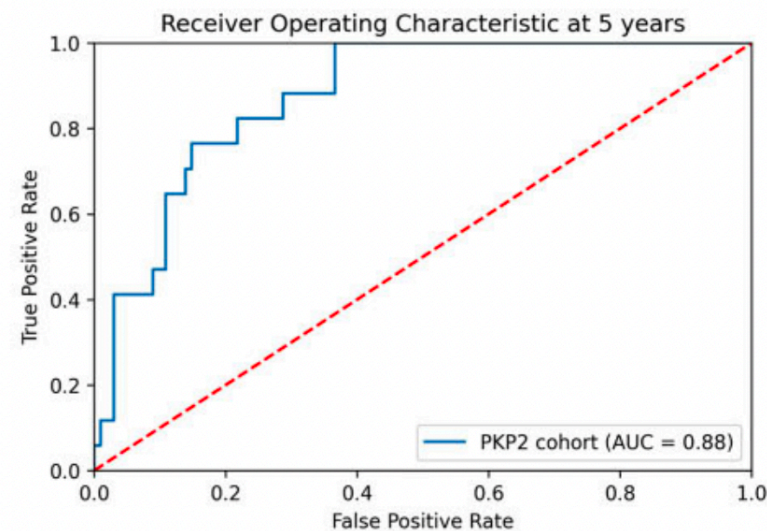
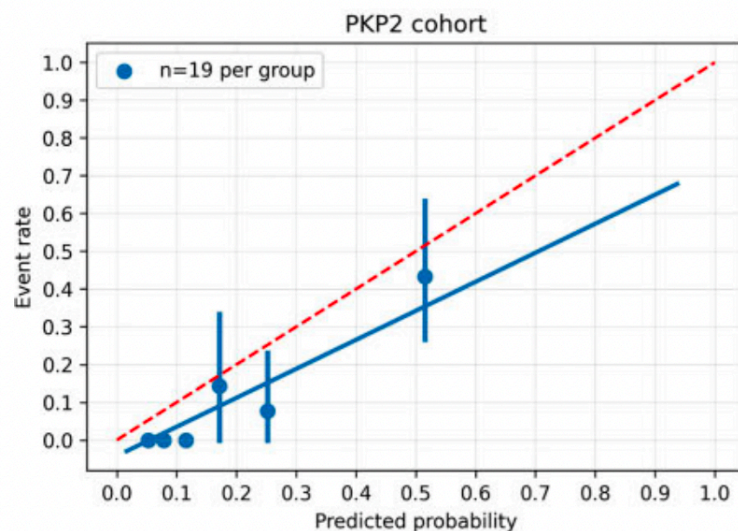


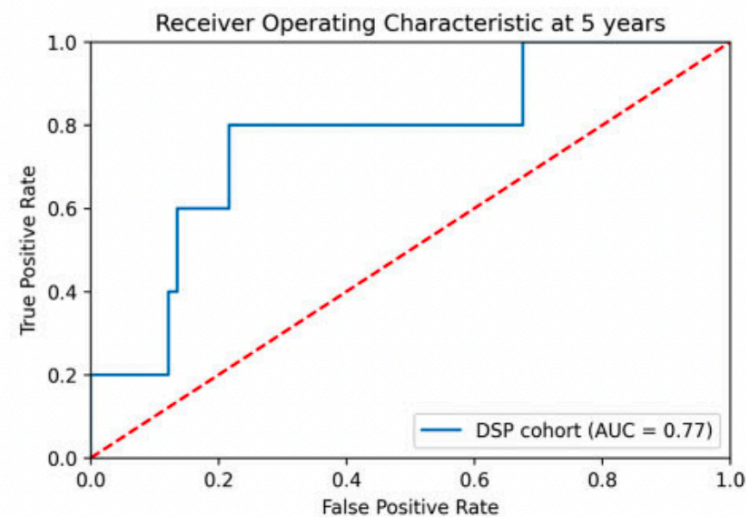
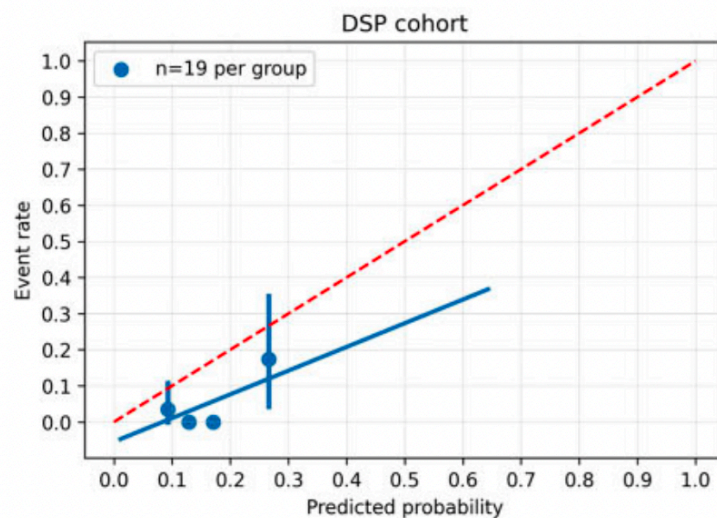
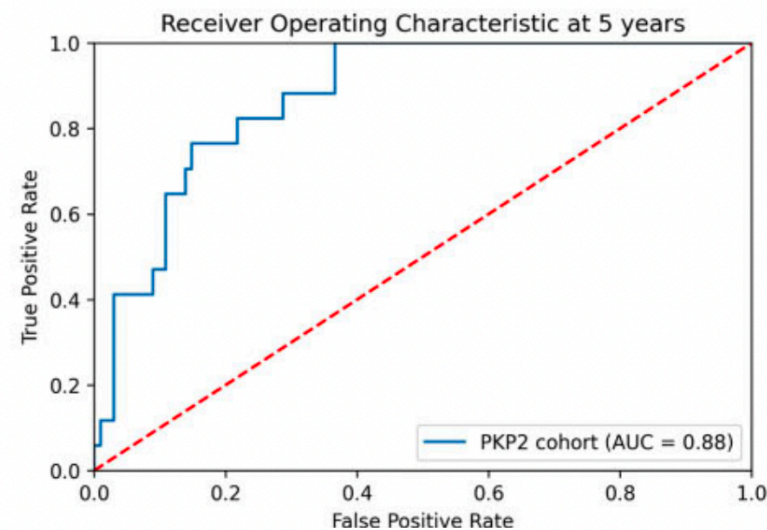
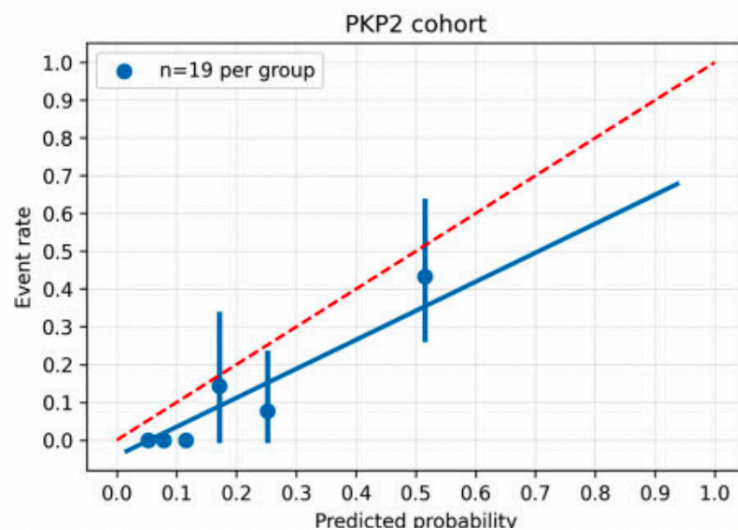
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CLINICAL RESEARCH
Heart failure and cardiomyopathies

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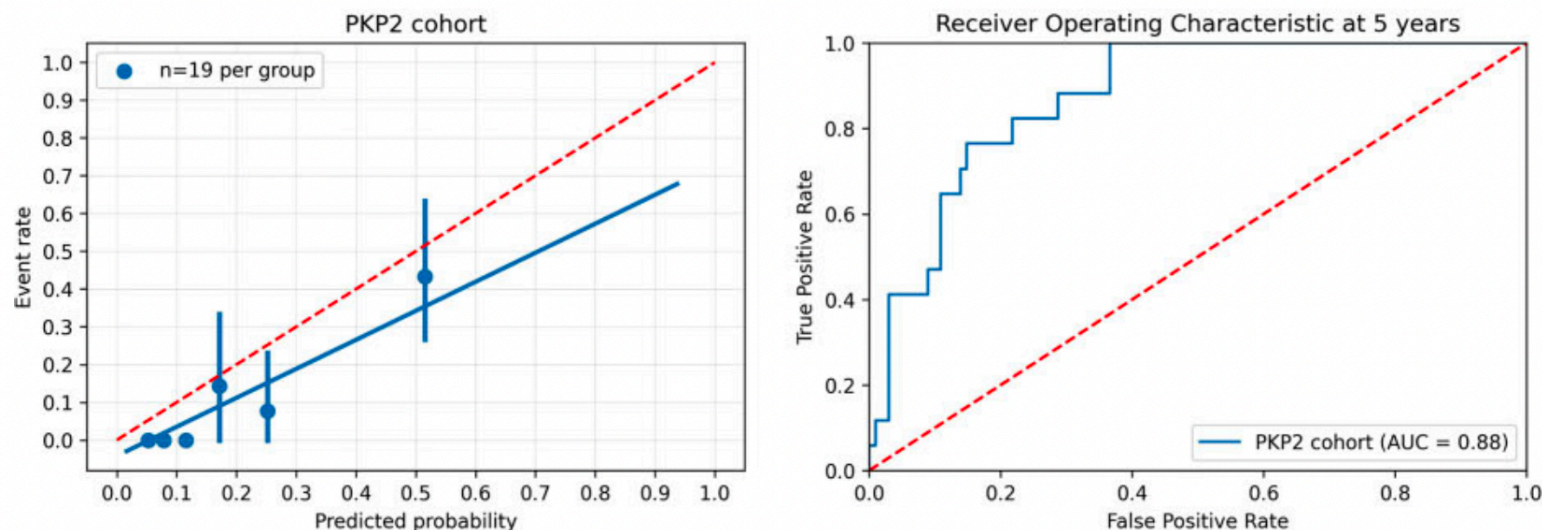


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The 2019 ARVC risk model performs reasonably well in gene-positive ARVC (particularly for PKP2) but is more limited in gene-elusive patients. Genotype should be included in future risk models for ARVC.

The updated 2019 ARVC risk calculator should be considered to aid individualized decision-making for ICD implantation in patients with ARVC.^{d,524,526,536-539}
PKP2

IIa

B

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5-year VA Risk:

Genetic Sex:

History of NSVT:

Left Ventricular Dysfunction (EF < 50%):

Right Ventricular Dysfunction (Moderate to Severe):

24 hour PVC Burden on Ambulatory Monitoring:

<https://www.dsp-risk.com/>

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Take Home Message

Patients harboring P/LP DSP demonstrate a distinct clinical phenotype, ECG derangement, frequent ventricular ectopy, and a high VA/HF risk. Inflammatory myocardial injury is common and causes an increase in patient risk for VA and HF hospitalization.

n = 800 patients with P/LP DSP variants

Clinical features of VA/HF risk on multivariable analysis



500+ PVC/24h

TWI in 3+ leads

Previous (N)SVT

LVEF ≤ 50%

High burden of adverse events



High VA and HF hospitalization rates (3.9%/yr and 1.8%/yr)

Almost 1/2 VA episodes are > 250 bpm

Unique characteristics of disease

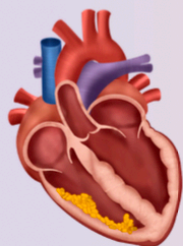


Myocardial injury episodes are common (8.7%) and associated with subsequent increases in VA (HR: 2.39) and HF (HR: 5.06)

Female patients experience higher rates of VA (HR: 1.55)

Multiple possible phenotypes

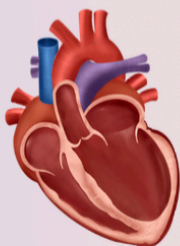
ARVC/TFC+ (36.8%)



VA:
6.5%/yr

HF:
2.1%/yr

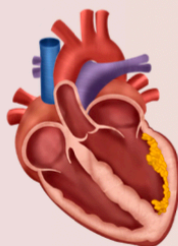
DCM (7.4%)



VA:
4.5%/yr

HF:
2.4%/yr

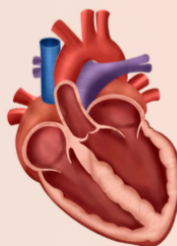
NDLVC (23.4%)



VA:
2.9%/yr

HF:
2.7%/yr

None (32.5%)



VA:
0.5%/yr

HF:
0.3%/yr



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CLINICAL RESEARCH

Heart failure and cardiomyopathies

Clinical features and outcomes in carriers of pathogenic desmoplakin variants

Alessio Gasperetti^{1,2,3,†}, Richard T. Carrick^{1†}, Alexandros Protonotarios⁴, Brittney Murray¹, Mikael Laredo^{5†}, Iris van der Schaaf^{3†}, Ronald H. Lekanne^{3†}, Petros Syrris⁴, Douglas Canine⁴, Crystal Tichnell¹, Chiara Cappelletto^{6†}, Marta Gigli^{6†}, Kristen Medo⁷, Ardan M. Saguner^{8,9}, Firat Duru^{8,9}, Nisha A. Gilotra¹, Stefan Zimmerman¹, Robyn Hyland¹⁰, Dominic J. Abrams¹⁰, Neal K. Lakdawala¹¹, Julia Cadrin-Tourigny¹², Mattia Targetti¹³, Iacopo Olivetto¹³, Maddalena Graziosi^{14†}, Moniek Cox¹⁵, Elena Biagini^{14†}, Philippe Charron^{3†}, Michela Casella¹⁶, Claudio Tondo^{17,18}, Momina Yazdani^{19,20}, James S. Ware^{19,20}, Sanjay K. Prasad^{19,20}, Leonardo Calò²¹, Eric D. Smith²², Adam S. Helms²², Sophie Hespé²³, Jodie Ingles²³, Harikrishna Tandri¹, Flavie Ader^{24,25}, Giovanni Peretto²⁶, Stacey Peters²⁷, Ari Horton²⁷, Jess Yao²⁷, Sven Dittmann^{28†}, Eric Schulze-Bahr^{28†}, Maria Qureshi²⁹, Katelyn Young²⁹, Eric D. Carruth²⁹, Chris Haggerty^{29,30}, Victoria N. Parikh³¹, Matthew Taylor⁷, Luisa Mestroni⁷, Arthur Wilde^{32,33†}, Gianfranco Sinagra⁵, Marco Merlo^{6†}, Estelle Gandjbakhch^{5†}, J. Peter van Tintelen^{2,34}, Anneline S.J.M. te Riele^{3,34†}, Perry M. Elliott⁴, Hugh Calkins¹, and Cynthia A. James¹

Table 21 High-risk genotypes and associated predictors of sudden cardiac death

Gene	Annual SCD rate	Predictors of SCD
DSP ^{185,186}	3–5%	LGE on CMR LVEF < 45%



5-year VA Risk:

Genetic Sex:

History of NSVT:

Non-Missense Mutation:

1st Degree AV Block:

2nd or 3rd Degree AV Block:

Left Ventricular Ejection Fraction:

[https://www.acm-risk.com/](https://www.acm-risk.com/Imna_risk.html)
[Imna_risk.html](https://www.acm-risk.com/Imna_risk.html)
Circulation

ORIGINAL RESEARCH ARTICLE

Development and Validation of a New Risk Prediction Score for Life-Threatening Ventricular Tachyarrhythmias in Laminopathies

ICD implantation should be considered in DCM/ HNDCM patients with a pathogenic mutation in *LMNA* gene, if the estimated 5-year risk of life-threatening VA is $\geq 10\%^c$ and in the presence of NSVT or LVEF < 50% or AV conduction delay.^{80,652,653}

Gene	Annual SCD rate	Predictors of SCD
<i>LMNA</i> ^{185,186,438,541,865,878,879}	5–10%	Estimated 5-year risk of life-threatening arrhythmia using <i>LMNA</i> risk score (https://Imna-risk-vta.fr)

Ila

B

ESC 2022
ESC 2023

In individuals with lamin A/C ACM and two or more of the following: LVEF <45%, NSVT, male sex, an ICD is reasonable (COR Ila, LOE B-NR).

In individuals with lamin A/C ACM and an indication for pacing, an ICD with pacing capabilities is reasonable (COR Ila, LOE C-LD).

HRS 2019



5-year VA Risk:

Genetic Sex:

History of NCVT:

Non-Missense Mutation:

1st Degree AV Block:

2nd or 3rd Degree AV Block:

Left Ventricular Ejection Fraction:

Timing of cardioverter-defibrillator implantation in patients with cardiac laminopathies—External validation of the *LMNA*-risk ventricular tachyarrhythmia calculator

Christine Rootwelt-Norberg, MD,^{*†} Alex Hørby Christensen, MD, PhD,^{‡§||}
Eystein T. Skjølsvik, MD,^{*†} Monica Chivulescu, MD,^{*†} Christoffer R. Vissing, MD,^{‡§}
Henning Bundgaard, MD, PhD,^{‡§} Eivind W. Aabel, MD,^{*†} Martin P. Bogsrud, MD, PhD,[¶]
Nina E. Hasselberg, MD, PhD,^{*†} Øyvind H. Lie, MD, PhD,^{*†}
Kristina H. Haugaa, MD, PhD^{*#**}



ESC

European Society
of Cardiology

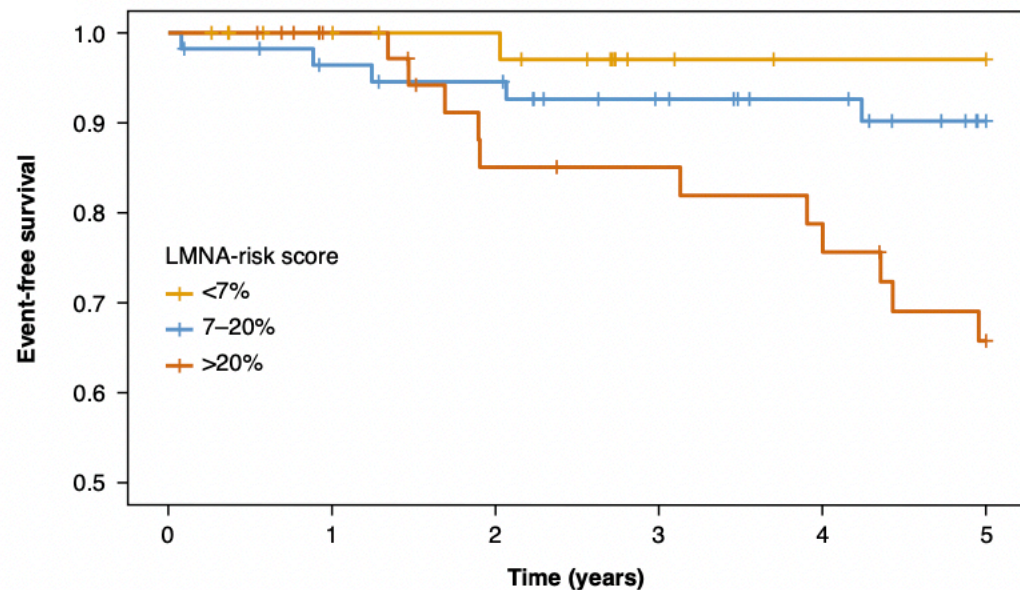
Europace (2025) 27, eua202
<https://doi.org/10.1093/europace/eua202>

RAPID COMMUNICATION

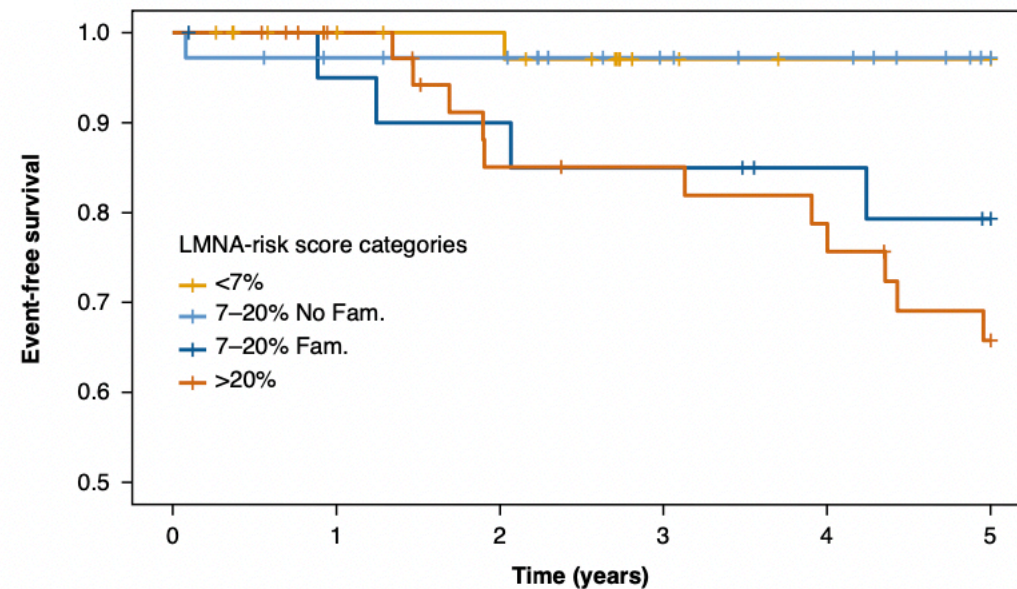
Family history of sudden cardiac death as a risk marker for ventricular arrhythmias in laminopathies

Gauthier Giordano ^{1,2,3}, Julie Proukhnitzky ^{1,4}, Frédéric Fer ⁵, Adrien Bloch⁶,
Marine Thuillot¹, Carole Maupain ¹, Isabelle Magnin-Poull ²,
Isabelle Jonveaux ⁴, Aurélien Palmyre ⁷, Agathe Bertinotti ⁴,
Nicolas Mansencal ⁸, Christian de Chillou ², Pascale Richard⁶,
Estelle Gandjbakhch ^{1,3,4}, and Philippe Charron ^{1,3,4,7*}





—	41	36	34	26	24	24
—	57	52	50	43	39	31
—	40	35	28	27	25	20

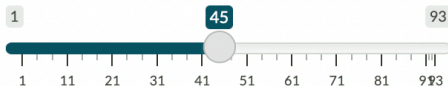


—	41	36	34	26	24	24
—	36	33	32	26	24	18
—	21	19	18	17	15	13
—	40	35	28	27	25	20

Family history had no discriminative value in low- or high-risk groups.



Age (years):



Sex:

Male ▼

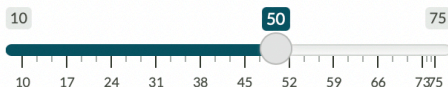
Non-sustained ventricular tachycardia (NSVT):

No ▼

History of syncope:

No ▼

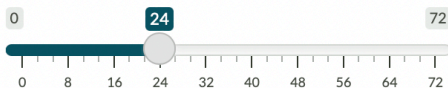
LVEF (%):



Select risk prediction window:

(Default 24 months)

Time in months:



Obtain Prediction

JAMA Cardiology | **Original Investigation**

Arrhythmic Risk Stratification of Carriers of Filamin C Truncating Variants

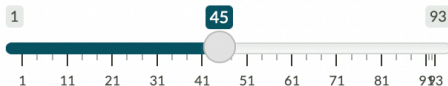
Filamin C Registry Consortium

<https://flnctv.shinyapps.io/RiskCalculator/>

Limited number of cardiac MRI tests in the FLNC Registry. Clinical judgement is advised in taking into account high-risk LGE pattern and other potential risk markers not adequately captured by the FLNC Risk Score



Age (years):



Sex:

Male

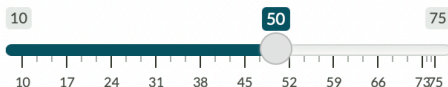
Non-sustained ventricular tachycardia (NSVT):

No

History of syncope:

No

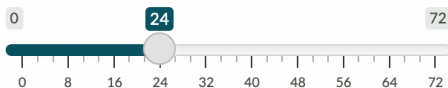
LVEF (%):



Select risk prediction window:

(Default 24 months)

Time in months:



Obtain Prediction

JAMA Cardiology | **Original Investigation**

Arrhythmic Risk Stratification of Carriers of Filamin C Truncating Variants

Filamin C Registry Consortium

<https://flnctv.shinyapps.io/RiskCalculator/>

Non-linear association between LVEF and arrhythmic risk (low risk for LVEF values greater than 58%, whereas the risk did not increase for decreasing LVEF values)

<i>FLNC</i> -truncating variants ^{866,867,880}	5–10%	LGE on CMR LVEF < 45%	
An ICD should be considered in patients with NDLVC with a genotype associated with high SCD risk and LVEF >35% in the presence of additional risk factors (see Table 21). ^{185,186,438,541,542,865–869,878–883}			IIa
An ICD may be considered in selected patients with NDLVC with a genotype associated with high SCD risk and LVEF >35% without additional risk factors (see Table 21).			IIb
			C

ESC 2023

In individuals with *FLNC* ACM and an LVEF <45%, an ICD is reasonable (COR IIa, LOE C-LD).

HRS 2019

ICD implantation should be considered in DCM/HNDCM patients with a LVEF <50% and ≥2 risk factors (syncope, LGE on CMR, inducible SMVT at PES, pathogenic mutations in *LMNA*,^d *PLN*, *FLNC*, and *RBM20* genes).

IIa

C

ESC 2022

<https://flnctv.shinyapps.io/RiskCalculator/>

Insert patient's information:

Age (years):



Sex:

Male

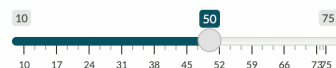
Non-sustained ventricular tachycardia (NSVT):

Yes

History of syncope:

No

LVEF (%):



Select risk prediction window:

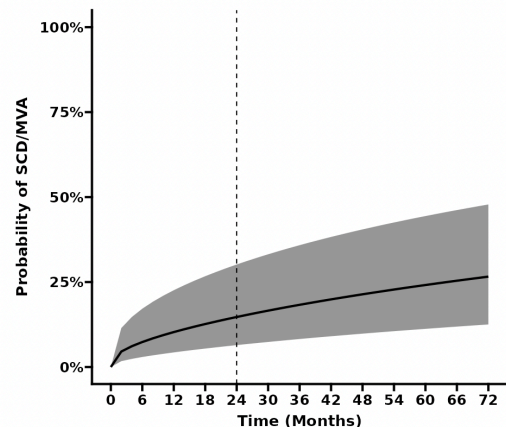
(Default 24 months)

Time in months:



Obtain Prediction

Predicted probability of SCD/MVA



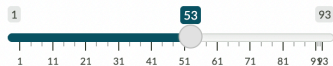
The predicted probability of SCD/MVA at 24 months is 14.7% (95% CI: 6.5-30.2).

Notes:

Although the incidence of sustained VA has been shown to increase in patients with LGE (Castrichini et al., 2024) the limited number of cardiac MRI tests in the FLNC Registry allowed to assess the potential contribution of LGE only in a subset of patients. Clinical judgement is advised in taking into account high-risk LGE pattern and other potential risk markers not adequately captured by the FLNC Risk Score: this remains an essential part of shared-decision making around ICD implantation even in low-risk FLNC patients. Phenotype-negative patients showed an overall low risk and therefore risk estimates should be interpreted in this context. The FLNCtv risk score has not yet been externally validated in an independent cohort of FLNC P/LP variant carriers.

Insert patient's information:

Age (years):



Sex:

Male

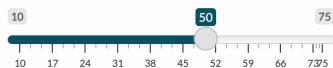
Non-sustained ventricular tachycardia (NSVT):

Yes

History of syncope:

No

LVEF (%):



Select risk prediction window:

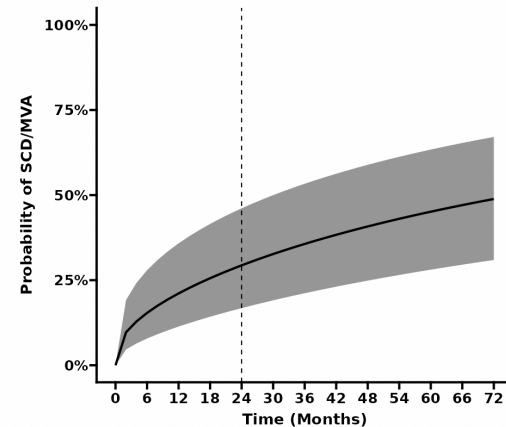
(Default 24 months)

Time in months:



Obtain Prediction

Predicted probability of SCD/MVA



The predicted probability of SCD/MVA at 24 months is 29.4% (95% CI: 16.8-46.1).

Notes:

Although the incidence of sustained VA has been shown to increase in patients with LGE (Castrichini et al., 2024) the limited number of cardiac MRI tests in the FLNC Registry allowed to assess the potential contribution of LGE only in a subset of patients. Clinical judgement is advised in taking into account high-risk LGE pattern and other potential risk markers not adequately captured by the FLNC Risk Score: this remains an essential part of shared-decision making around ICD implantation even in low-risk FLNC patients. Phenotype-negative patients showed an overall low risk and therefore risk estimates should be interpreted in this context. The FLNCtv risk score has not yet been externally validated in an independent cohort of FLNC P/LP variant carriers.

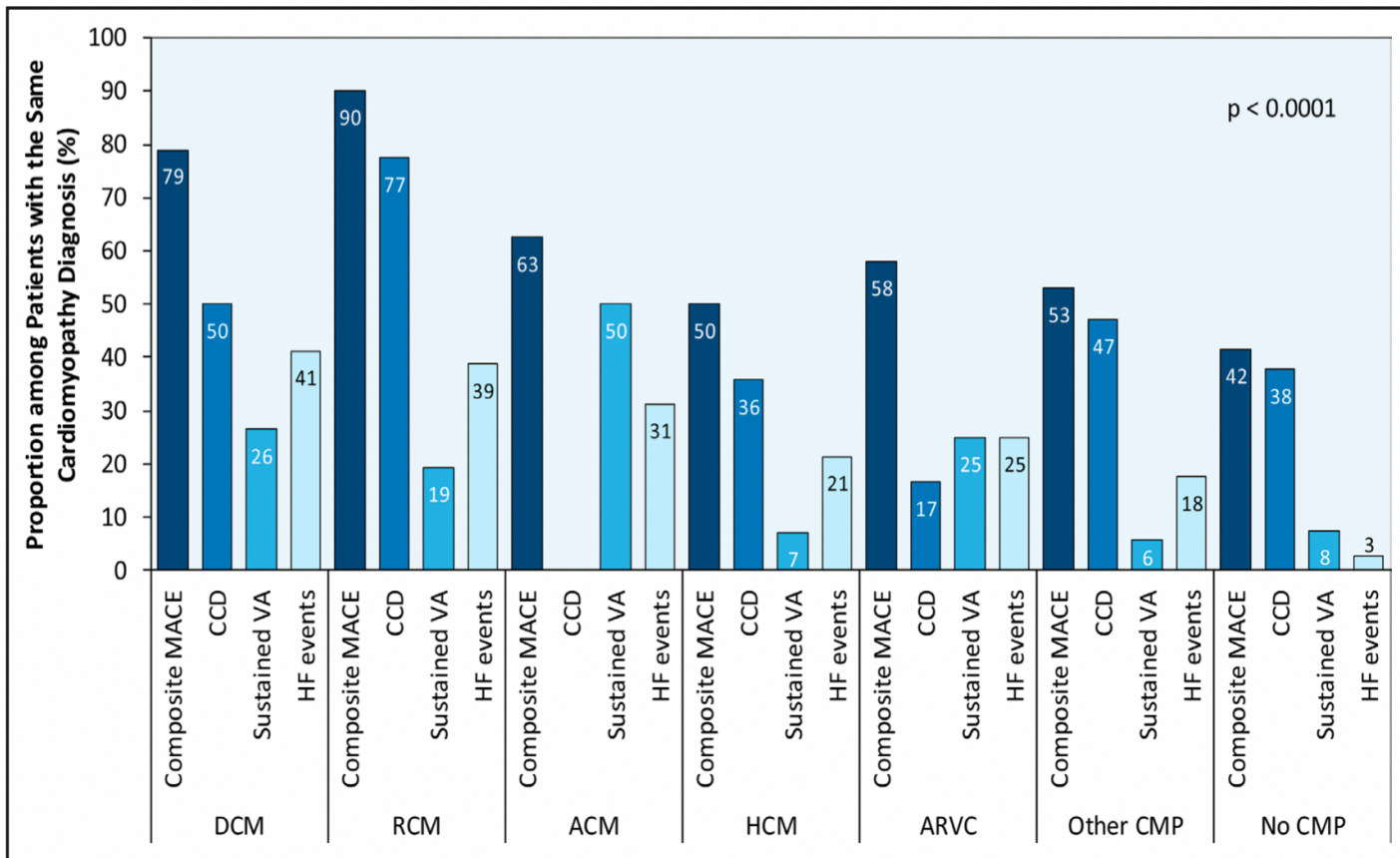
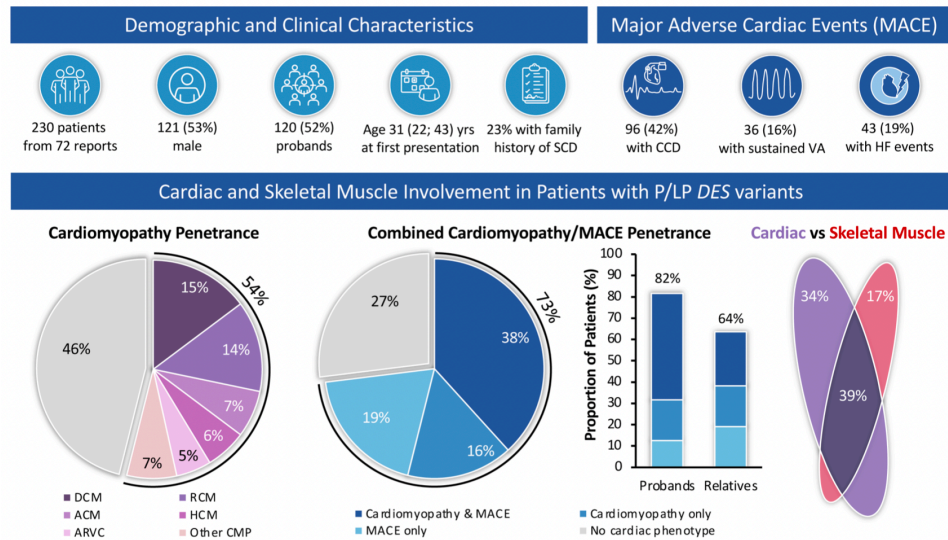


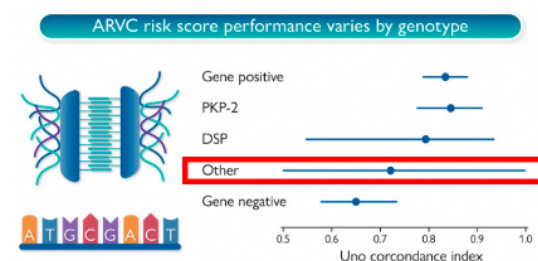
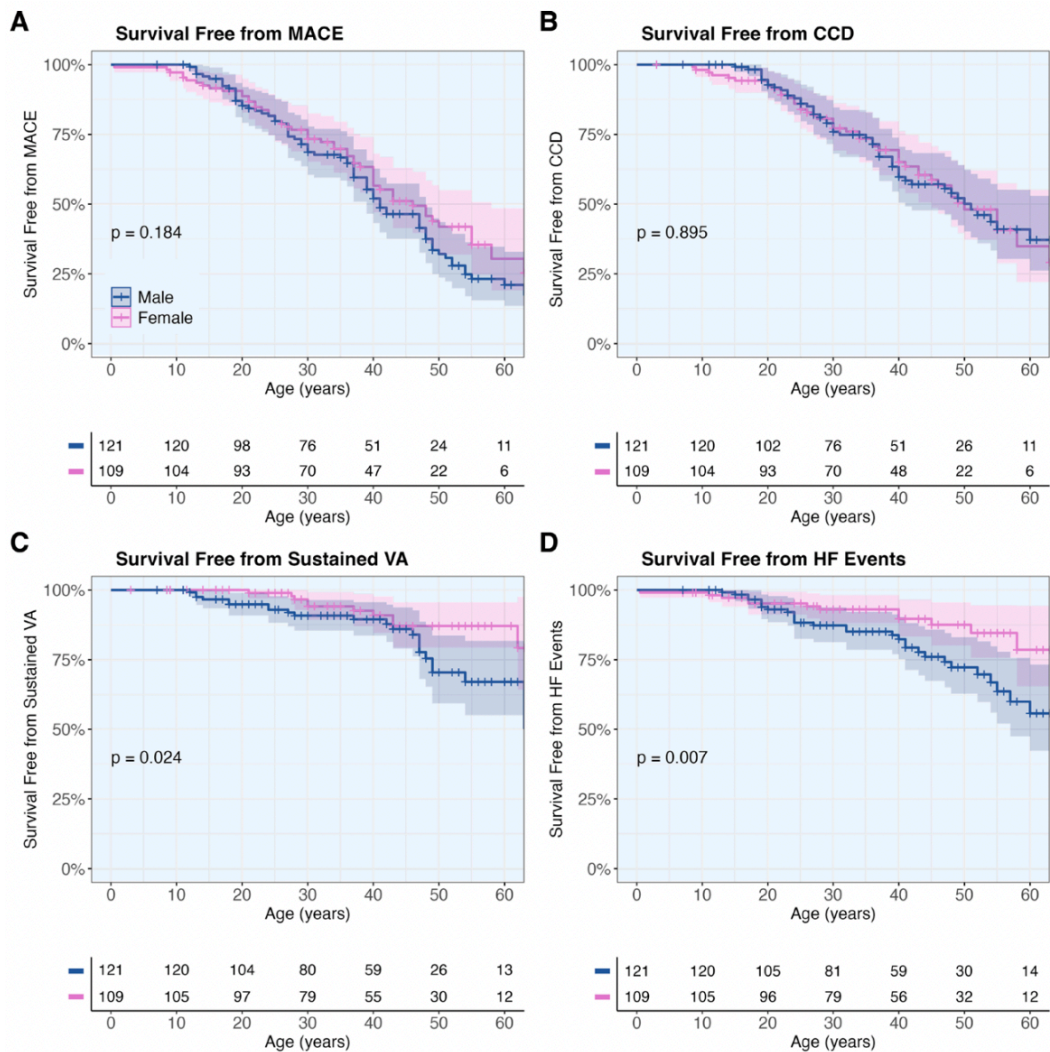
Meta-Analysis > Circ Genom Precis Med. 2025 Apr;18(2):e004878.

doi: 10.1161/CIRCGEN.124.004878. Epub 2025 Feb 19.

Natural History, Phenotype Spectrum, and Clinical Outcomes of Desmin (*DES*)-Associated Cardiomyopathy

Babken Asatryan¹, Marina Rieder², Brittney Murray¹, Steven A Muller^{1 3 4}, Crystal Tichnell¹, Alessio Gasperetti¹, Richard T Carrick¹, Emily Joseph⁵, Doris G Leung⁶, Annelise S J M Te Riele^{3 4 7}, Stefan L Zimmerman⁸, Hugh Calkins¹, Cynthia A James^{# 1}, Andreas S Barth^{# 1}





LMNA RISK CALCULATOR

5-year VA Risk:

Genetic Sex:

History of NSVT:

Non-Missense Mutation:

1st Degree AV Block:

2nd or 3rd Degree AV Block:

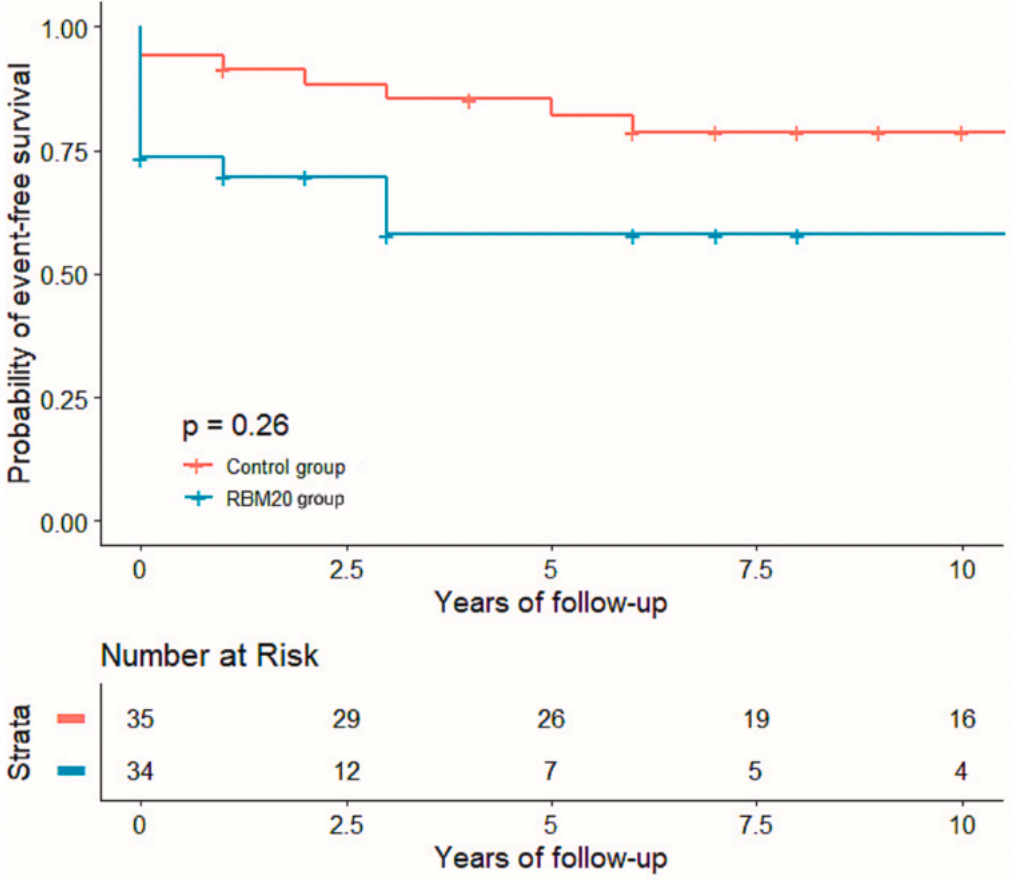
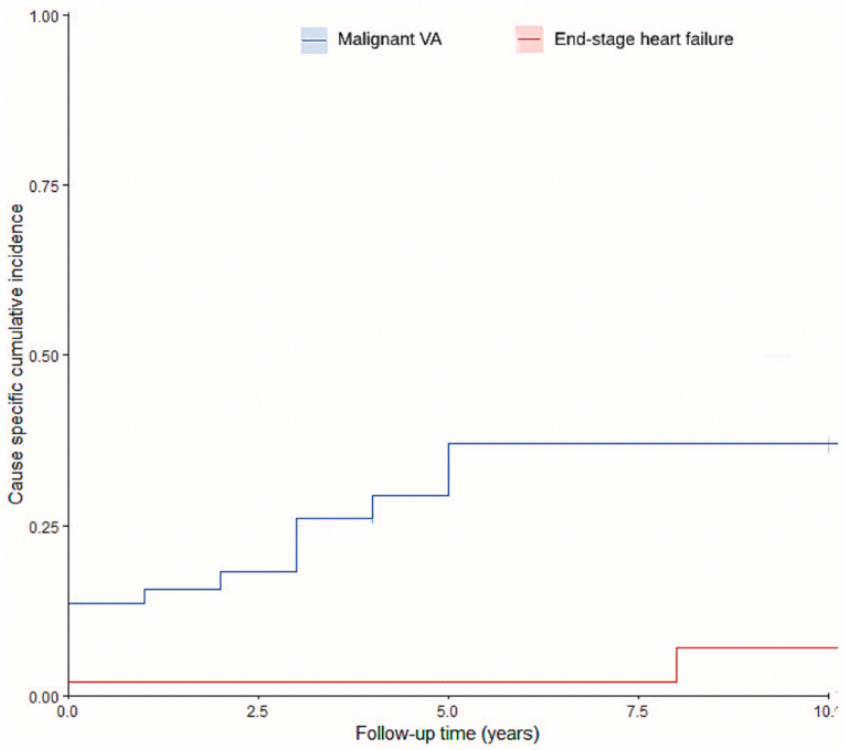
Left Ventricular Ejection Fraction:

EXTENSIVE LGE
FAMILY HISTORY



High incidence of malignant arrhythmias and heart failure in patients with *RBM20*-associated cardiomyopathy: A multicenter cohort study and review of the literature

Martijn Tukker^a, Wouter P. te Rijdt^b, Ahmad S. Amin^c, Deborah J. Morris-Rosendahl^{d,e}, Alexander Hirsch^{a,f}, Yael Ben-Haim^g, Arjan C. Houweling^h, Amanda Varnavaⁱ, Elijah R. Behr^g, Matthew Edwards^d, Alexander Vanmaele^a, Aida Hajdarpasic^j, Jan von der Thüsen^k, Michelle Michels^a, Rudolf A. de Boer^a, Marjon A. van Slegtenhorst^b, Kadir Caliskan^{a,*}



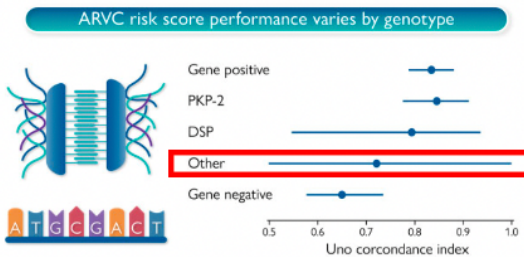
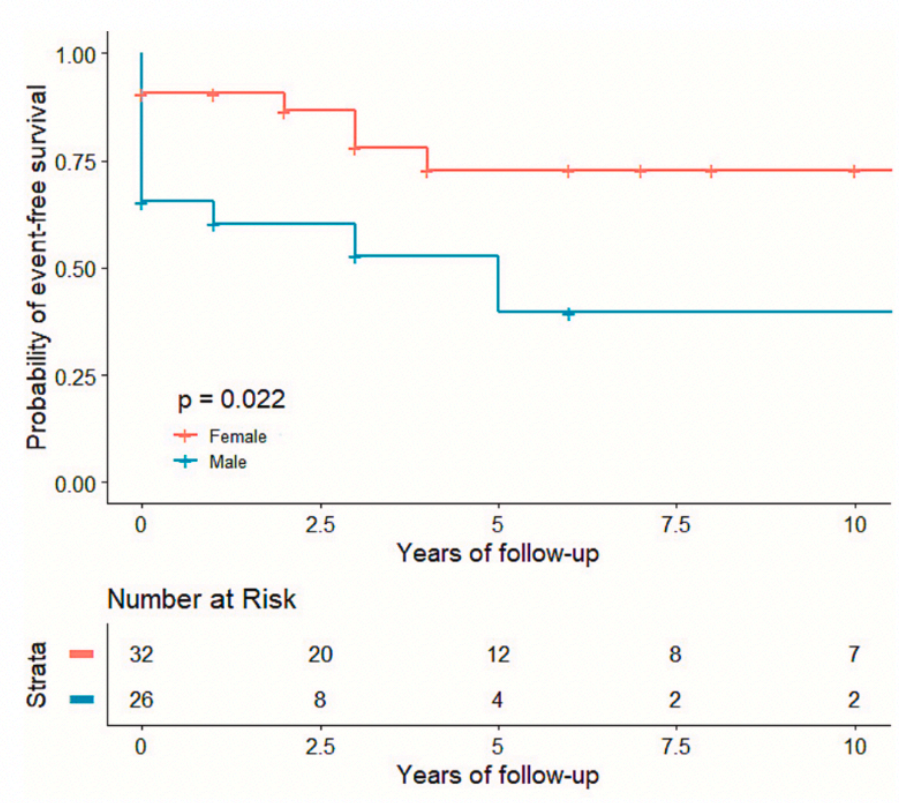
Kaplan-Meier curve for composite endpoint in RBM20 vs DCM control groups.

Fig. 1. a. Kaplan-Meier curve for the long-term outcome for VA vs end-stage HF in RBM20 patients.



High incidence of malignant arrhythmias and heart failure in patients with *RBM20*-associated cardiomyopathy: A multicenter cohort study and review of the literature

Martijn Tukker^a, Wouter P. te Rijdt^b, Ahmad S. Amin^c, Deborah J. Morris-Rosendahl^{d,e}, Alexander Hirsch^{a,f}, Yael Ben-Haim^g, Arjan C. Houweling^b, Amanda Varnavaⁱ, Elijah R. Behr^g, Matthew Edwards^d, Alexander Vanmaele^a, Aida Hajdarpasic^j, Jan von der Thüsen^k, Michelle Michels^a, Rudolf A. de Boer^a, Marjon A. van Slegtenhorst^b, Kadir Caliskan^{a,*}



LMNA RISK CALCULATOR

5-year VA Risk:

Genetic Sex:

←

History of NSVT:

←

Non-Missense Mutation:

← **MISSENSE**

1st Degree AV Block:

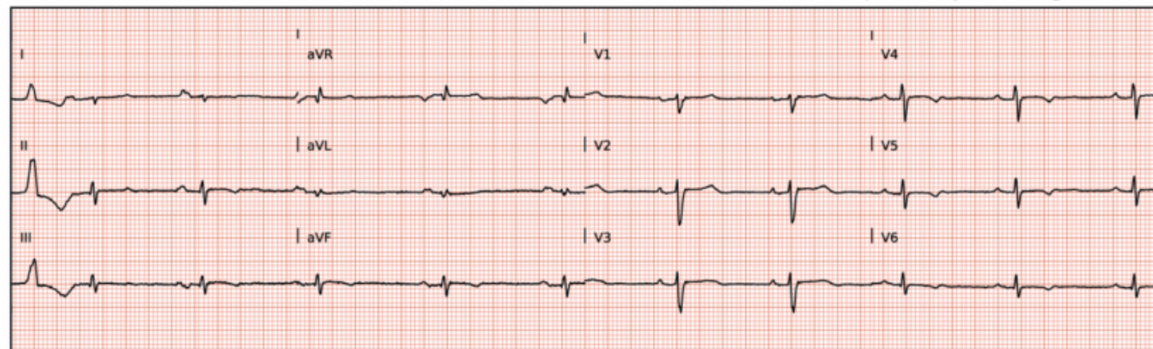
←

2nd or 3rd Degree AV Block:

← **30-60% vs 2%**

Left Ventricular Ejection Fraction:

←



Prediction of ventricular arrhythmia in phospholamban p.Arg14del mutation carriers—reaching the frontiers of individual risk prediction

Tom E Verstraelen^{1 2}, Freyja H M van Lint^{2 3}, Laurens P Bosman⁴, Remco de Brouwer⁵, Virginnio M Proost¹, Bob G S Abeln¹, Karim Taha⁴, Aeilko H Zwinderman⁶, Cathelijne Dickhoff⁷, Toon Oomen⁸, Bas A Schoonderwoerd⁹, Gerardus P Kimman¹⁰, Arjan C Houweling², Juan R Gimeno-Blanes^{11 12}, Folkert W Asselbergs^{4 13}, Paul A van der Zwaag¹⁴, Rudolf A de Boer⁵, Maarten P van den Berg⁵, J Peter van Tintelen^{2 3}, Arthur A M Wilde^{1 12}

Long-term reliability of the phospholamban (PLN) p. (Arg14del) risk model in predicting major ventricular arrhythmia: a landmark study

Myrthe Y C van der Heide¹, Tom E Verstraelen¹, Freyja H M van Lint^{2 3}, Laurens P Bosman⁴, Remco de Brouwer⁵, Virginnio M Proost¹, Esmée van Drie³, Karim Taha⁴, Aeilko H Zwinderman⁶, Cathelijne Dickhoff⁷, Bas A Schoonderwoerd⁸, Tjeerd Germans⁹, Arjan C Houweling², Juan R Gimeno-Blanes^{10 11}, Paul A van der Zwaag¹², Rudolf A de Boer¹³, Moniek G P J Cox⁵, J Peter van Tintelen^{3 11}, Arthur A M Wilde^{1 11}

Age-related penetrance of phospholamban p.Arg14del cardiomyopathy

Tom E Verstraelen^{1 2}, Freyja H M van Lint³, Remco de Brouwer⁴, Virginnio M Proost^{1 2}, Esmée van Drie³, Laurens P Bosman⁵, Lotte Weverink⁴, Karim Taha⁵, Thais Bueren^{1 2}, Aeilko H Zwinderman⁶, Cathelijne Dickhoff⁷, Toon Oomen⁸, Bas A Schoonderwoerd⁹, Tjeerd Germans¹⁰, Arjan C Houweling¹¹, Juan R Gimeno-Blanes^{12 13}, Folkert W Asselbergs^{1 2}, Paul A van der Zwaag¹⁴, Anneline S J M Te Riele^{5 13}, Rudolf A de Boer^{4 13}, Maarten P van den Berg⁴, J Peter van Tintelen^{3 13}, Arthur A M Wilde^{1 2 13}

PLN RISK CALCULATOR

The PLN Risk Calculator provides patients without prior sustained VA who have the pathogenic PLN (Phospholamban) p.Arg14del founder variant with individualized estimates of their risk for developing sustained ventricular arrhythmias in the 5-year period following their initial clinical assessment. These predictions are based on the previously published risk model from [Verstraelen et al.](#)

5-year VA Risk:

Low Amplitude QRS on ECG:

Left Ventricular Ejection Fraction:

T-Wave Inversions (Anterior + Inferior Leads):

24 hour PVC Burden on Ambulatory Monitoring:



Features of the electrocardiogram in *TMEM43* p.S358L arrhythmogenic cardiomyopathy ^e

Stephen A. Duffett, MD,¹ Chris Compton, MSc,¹ Kieran Vasanthan, MD,¹ Ian Short, MD,¹ Harinder Pal Gill, MD,¹ Terry-Lynn Young, PhD,² Sean P. Connors, MD, DPhil,¹ Kathleen A. Hodgkinson, PhD^{2,3}

Highly penetrant - Highly sex influenced

- In males, SCD may precede the onset of symptoms. PVCs on Holter is often the only abnormality seen in males to occur prior to death.
- In females, symptoms generally precede SCD
- The presence of *TMEM43* p.S358L requires ICD therapy in males from late adolescence/ early adulthood.

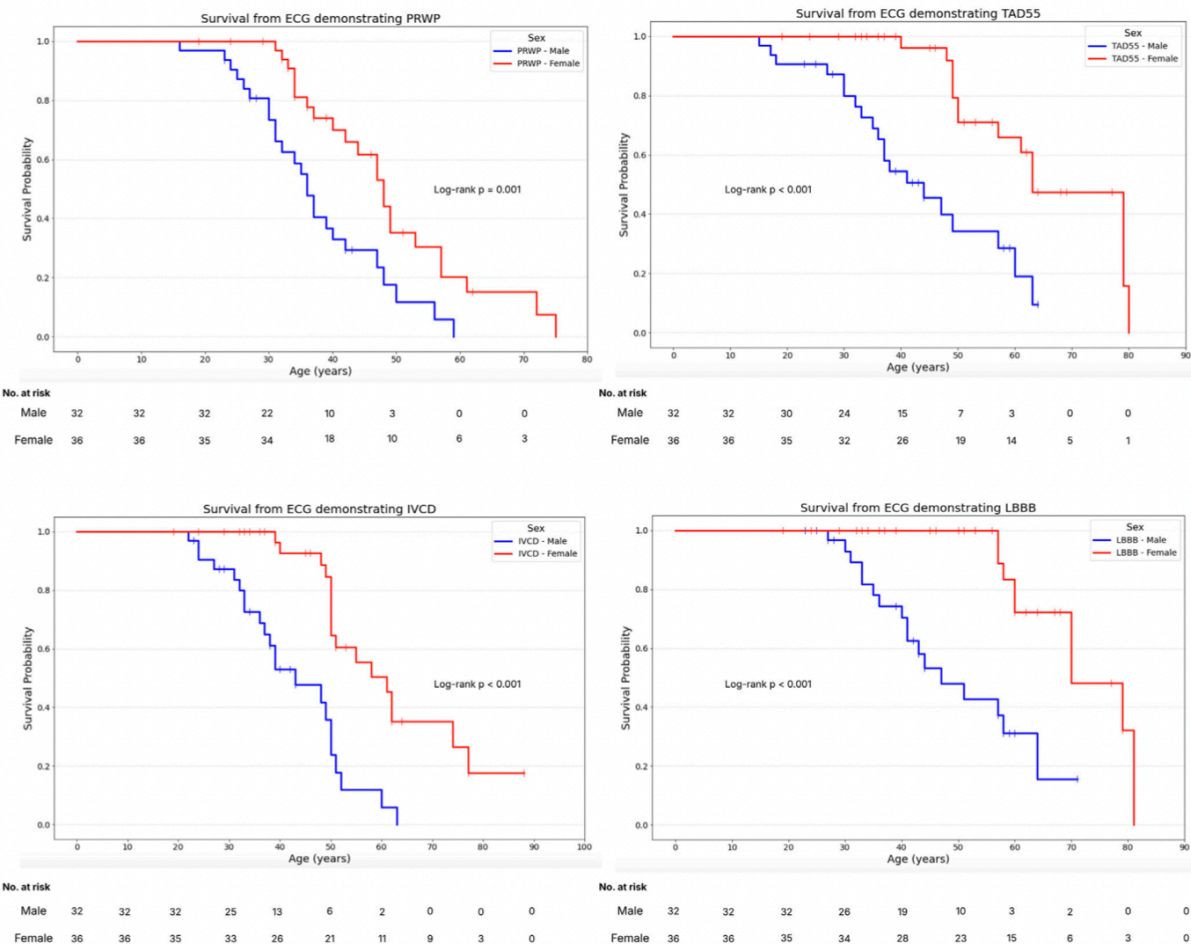


Figure 4
Kaplan-Meier survival curves for age at detection of the typical electrocardiogram (ECG) features for male vs female patients with *TMEM43* p.S358L arrhythmogenic cardiomyopathy. IVCD = intraventricular conduction delay; LBBB = left bundle branch block; PRWP = poor R-wave progression; TAD55 = terminal activation duration ≥ 55 ms.



- Expanded concept: from ARVC to broader NICM with high arrhythmic risk
- Genetics: from classical ARVC linked to desmosomal mutations to broader ACM forms involving also non-desmosomal genes
- Identifying specific ACM genotypes impacts patient care, particularly in risk assessment for LAEs and SCD.
- Genotype-specific risk prediction tools are being developed to assess individual arrhythmia risks.
- Gene-elusive patients: disease-level (ARVC/NDLVC) risk models

