3rd PORTO MEETING 2020
September, 18th - 19th

ARRHYTHMO "GENETIC" CARDIOMYOPATHIES: PERSONALIZING SUDDEN DEATH RISK STRATIFICATION

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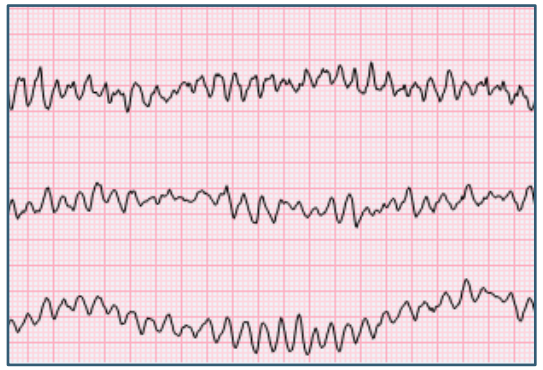
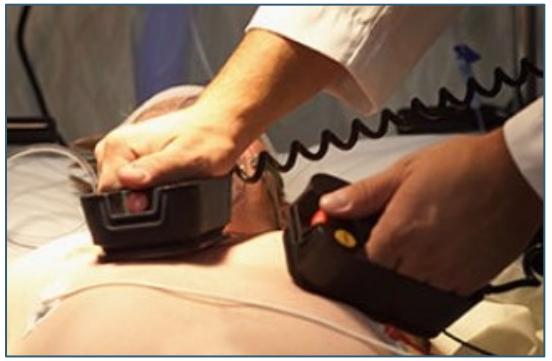
SUMMARY

- ✓ Sudden cardiac death in non-ischemic dilated cardiomyopathy
- ✓ New concepts – the arrhythmogenic cardiomyopathies
- ✓ Personalized arrhythmic risk assessment
- ✓ Clinical, electrocardiographic, electrophysiological and imaging parameters
- ✓ Importance of genetic profiling in sudden death risk stratification
- ✓ Conclusions

SUDDEN CARDIAC DEATH IN (NON-ISCHAEMIC) DILATED CARDIOMYOPATHY: A CHALLENGING ISSUE

- Three-year mortality remains high (12-20%) resulting from heart failure or arrhythmic sudden cardiac death (SCD).
- Incidence of SCD in dilated cardiomyopathy (DCM) patients is ~1.5/100 PA.
- DCM accounts for a substantial proportion of SCD specially among people of working age (younger, less comorbidity, lower mortality risk from other causes).





Halliday BP, Circulation 2017
Cannatà A, Heart 2020

SUDDEN CARDIAC DEATH IN (NON-ISCHAEMIC) DILATED CARDIOMYOPATHY: A CHALLENGING ISSUE

Study	n	Inclusion Criteria	Intervention	Follow-Up (Median), mo	All-Cause Mortality	Sudden Cardiac Death
CAT[3]	104	LVEF <30% NYHA II–III	ICD vs OMT	23	Terminated early	
AMIOVIRT[4]	103	LVEF ≤35% NYHA I–III NSVT	ICD vs amio	24	Terminated early	
SCD-HeFT (DCM cohort)[5]	1211	LVEF <35% NYHA II–III	ICD vs OMT vs amio	46	I, 21.4%; C, 27.9% (5 y) HR, 0.73; 95% CI, 0.50–1.07; *P*=0.06	
DEFINITE[6]	458	LVEF <36% NYHA I–III NSVT or PVCs	ICD vs OMT	29	I, 12.2%; C, 17.4% HR, 0.65; 95% CI, 0.40–1.06; *P*=0.08	I, 1.3%; C, 6.1% HR, 0.20; 95% CI, 0.06–0.71; *P*=0.006
DANISH[7]	1116	LVEF <35% NYHA II–III (IV if CRT) NT-proBNP >200pg/mL	ICD vs OMT	68	I, 21.6%; C, 23.4%; HR, 0.87; 95% CI, 0.68–1.12; *P*=0.28	I, 4.3%; C, 8.2% HR, 0.50; 95% CI, 0.31–0.82; *P*=0.005

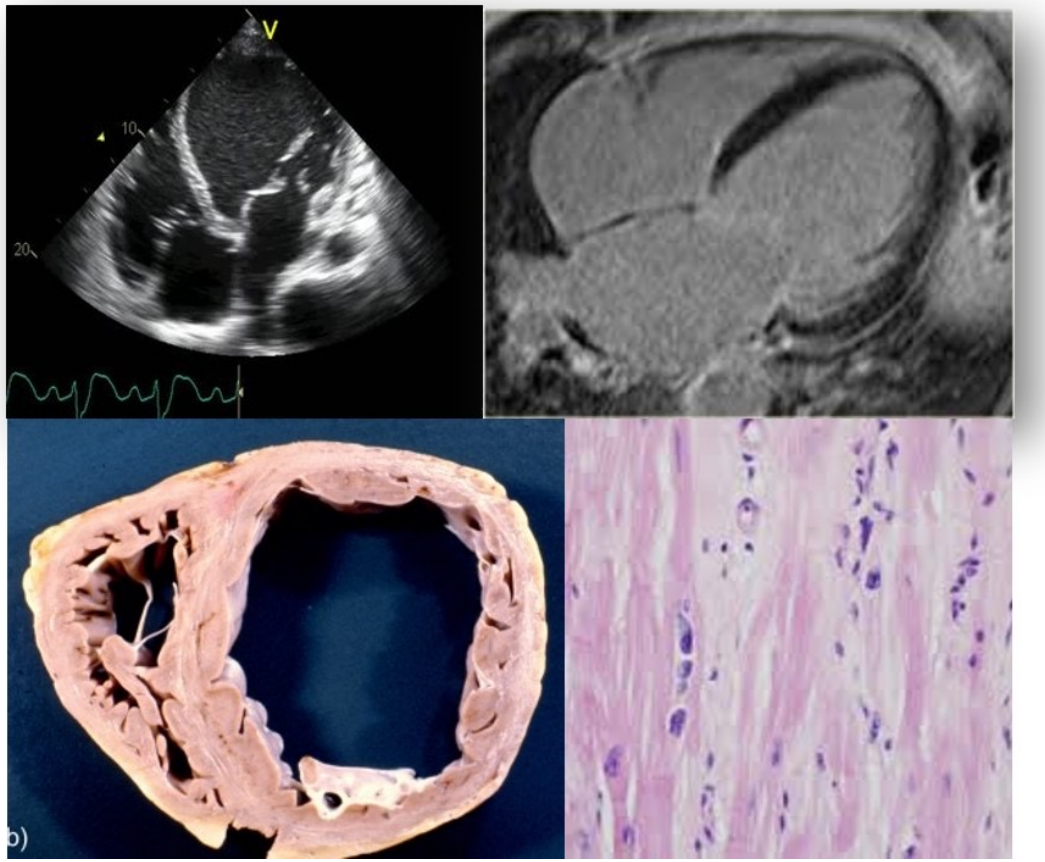
Halliday BP, Circulation 2017

SUDDEN CARDIAC DEATH IN (NON-ISCHAEMIC) DILATED CARDIOMYOPATHY: A CHALLENGING ISSUE

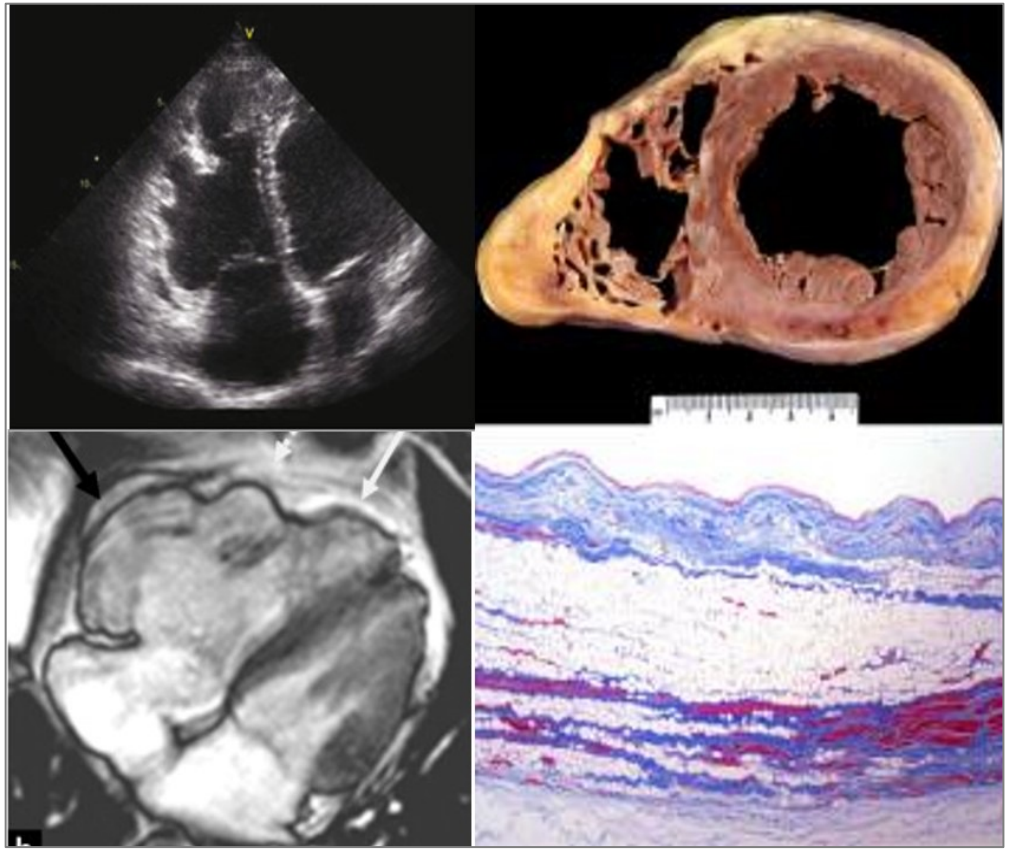
- Poor sensitivity and specificity of left ventricular ejection fraction (LVEF) for predicting SCD:
  - High proportion of cardiac arrest in patients with LVEF > 35%
  - Low incidence of appropriate ICD therapies
- Complications of ICD, inappropriate shocks and costs
- Inherent subjectivity in assessing LVEF and NYHA
- Up to 40% experience reverse remodelling under treatment

Halliday BP, Circulation 2017
Cannatà A, Heart 2020

CLASSIC DEFINITIONS

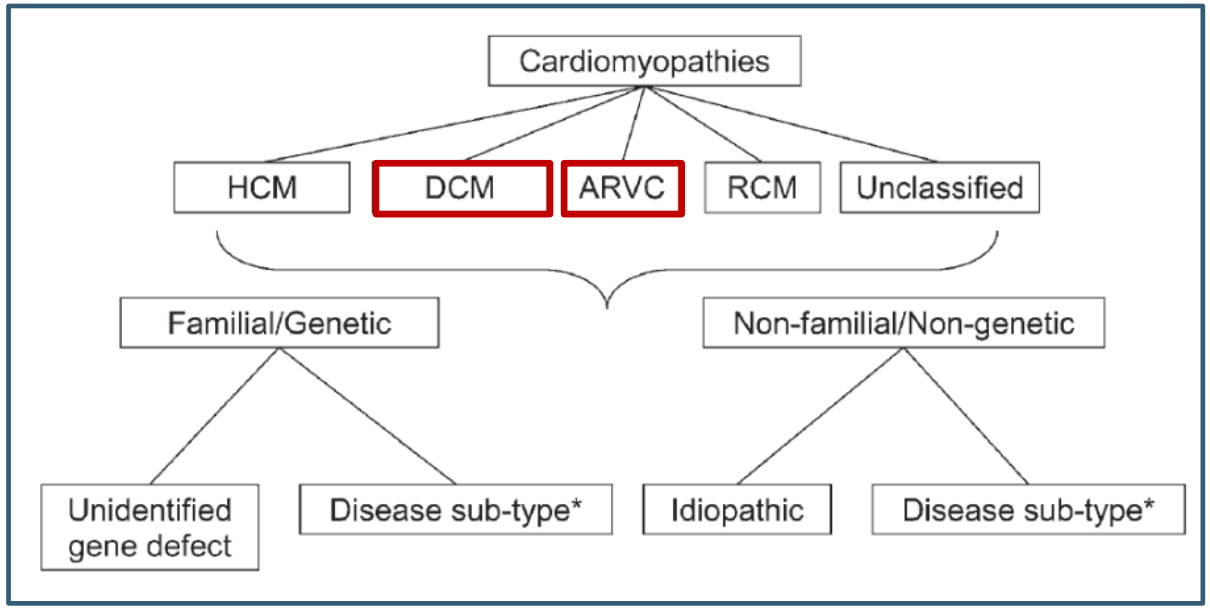


Dilated cardiomyopathy

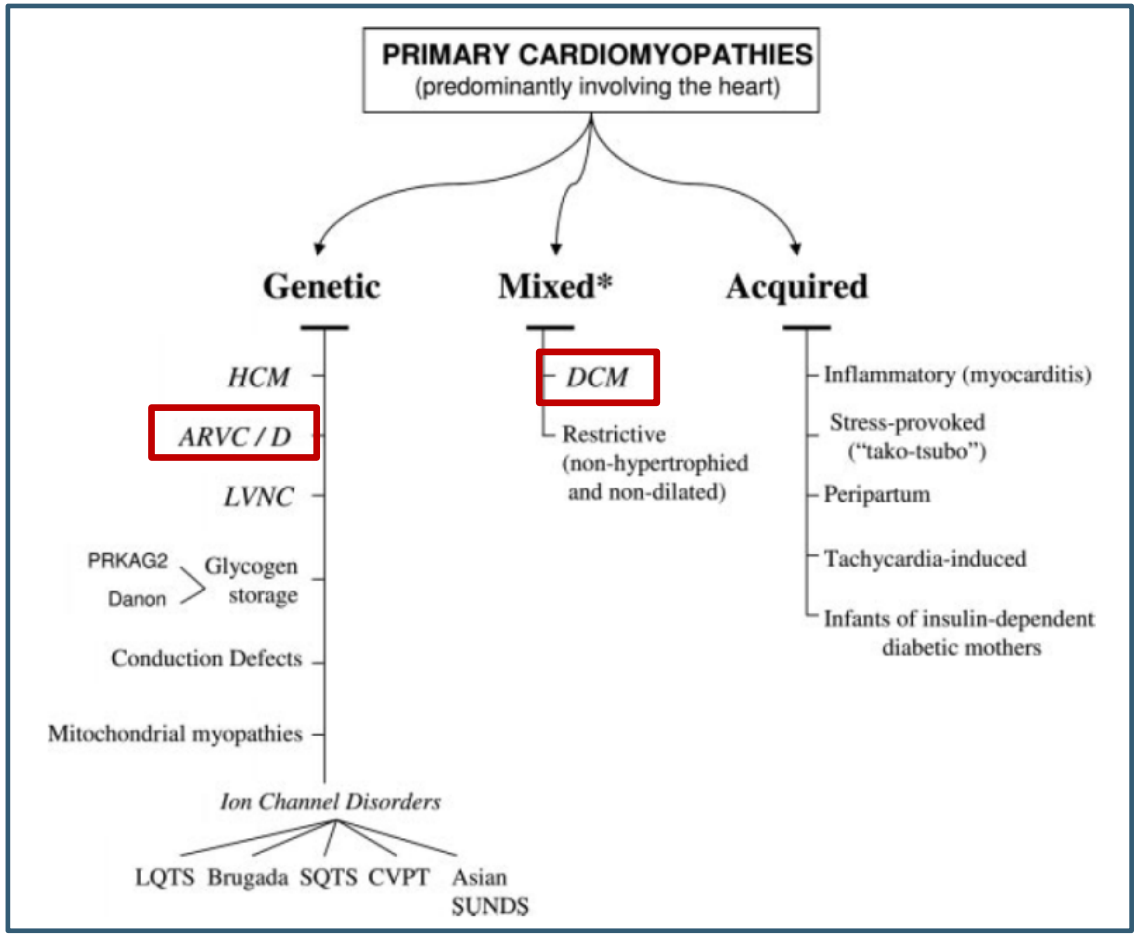


Arrhythmogenic (right ventricular) cardiomyopathy

CLASSIFICATION OF CARDIOMYOPATHIES

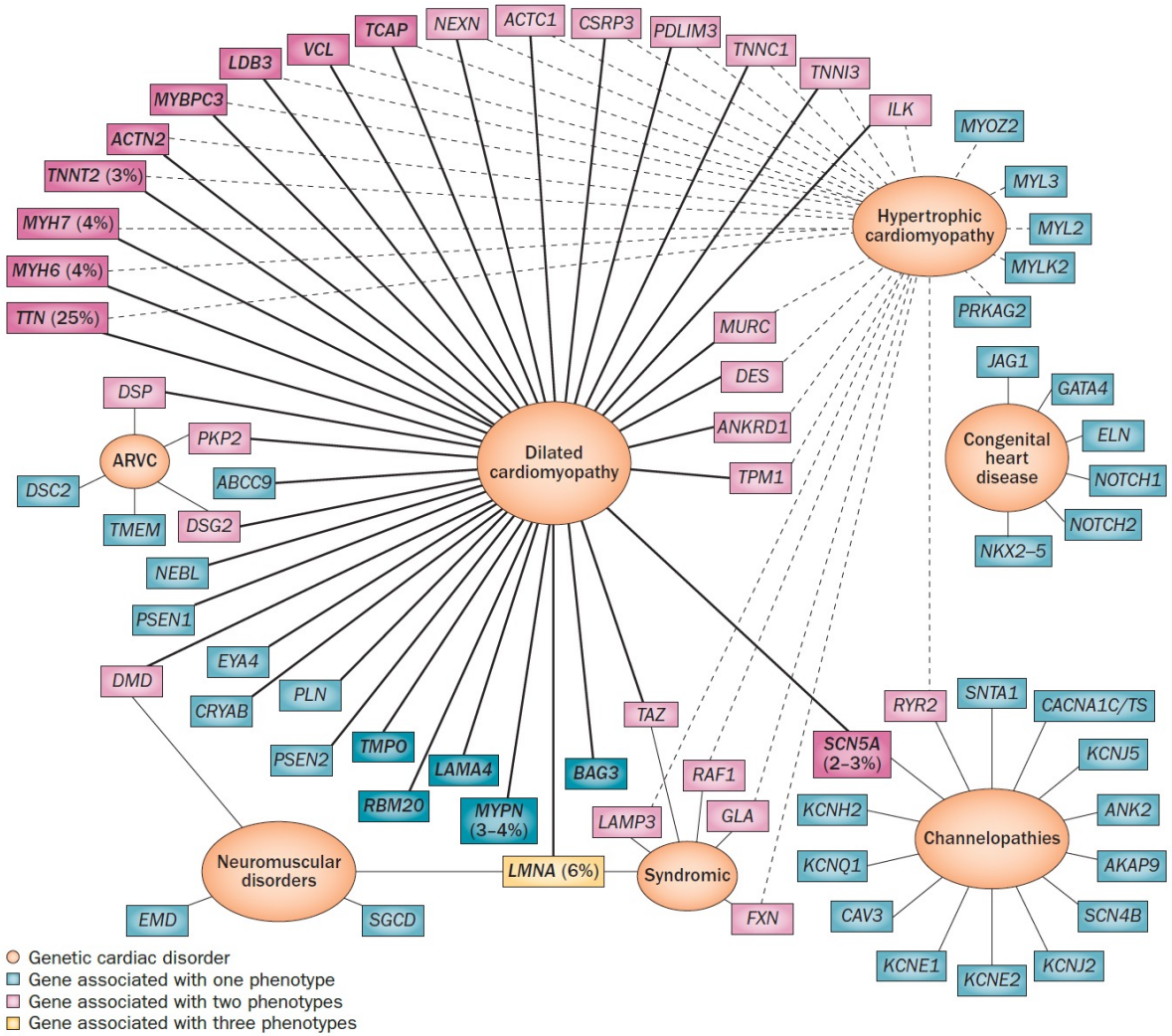


Elliot P, EHJ 2008

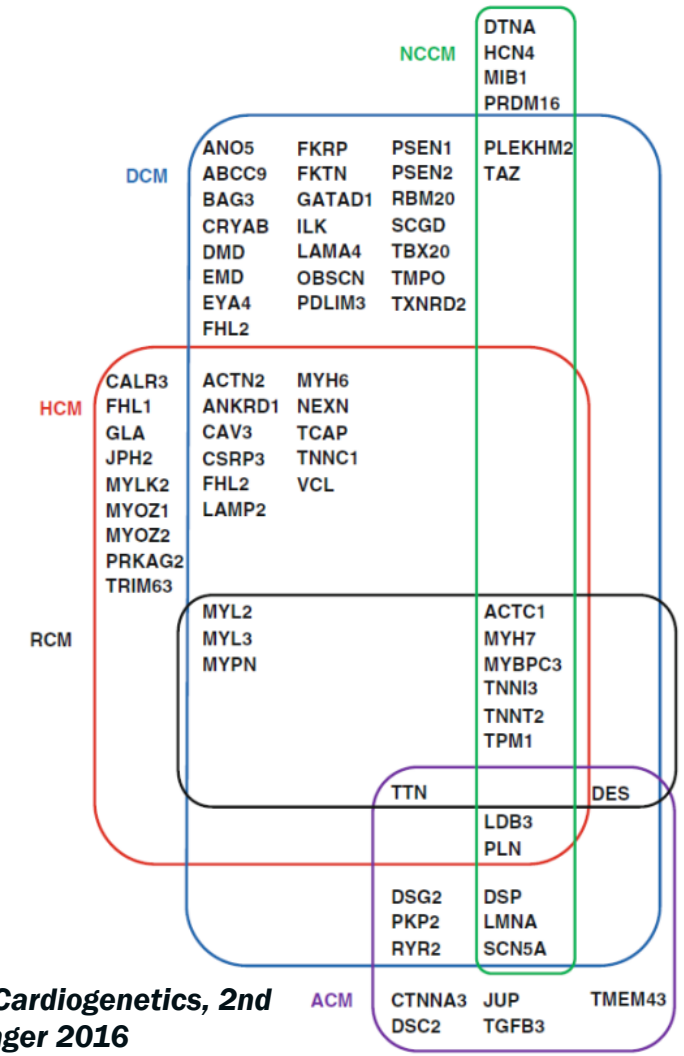


Maron BJ, Circ 2006

Genetic heterogeneity – numerous genetic variants, in multiple genes, with great overlap between "different" cardiomyopathies

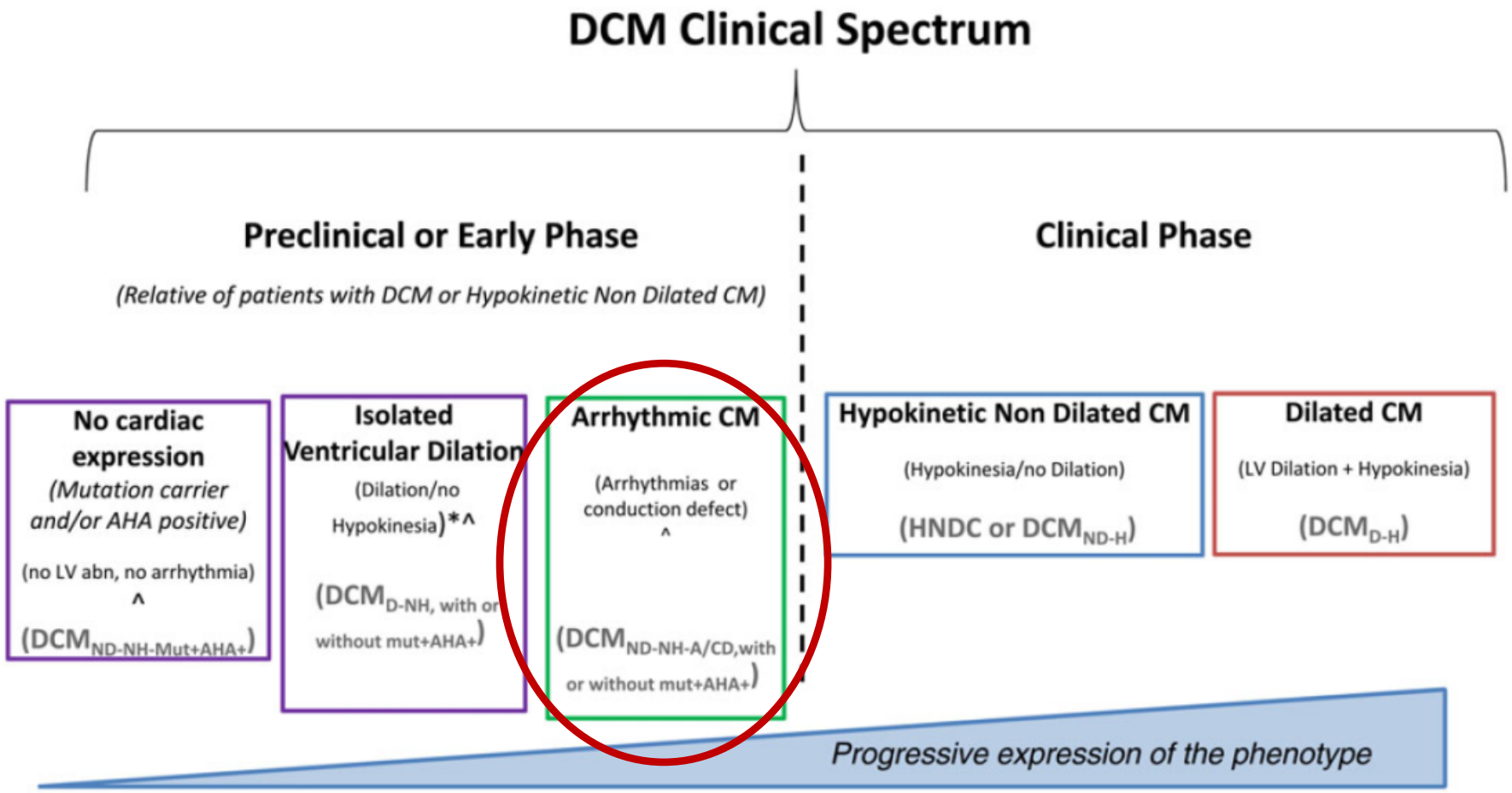


Hershberg RE, Nature 2013



Clinical Cardiogenetics, 2nd Ed. Springer 2016

ESC *NEW* DEFINITION OF DILATED CARDIOMYOPATHY

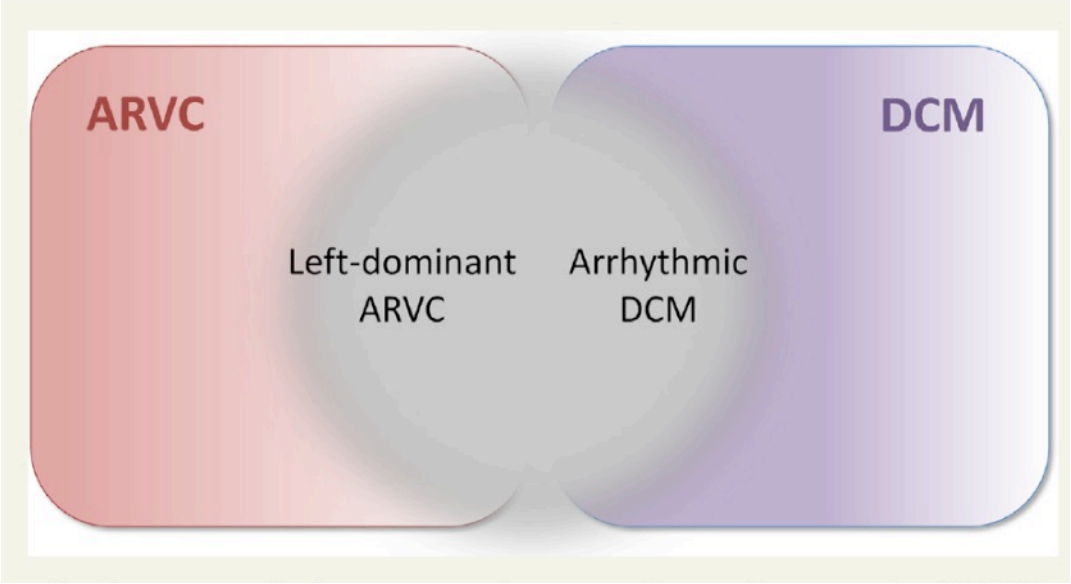


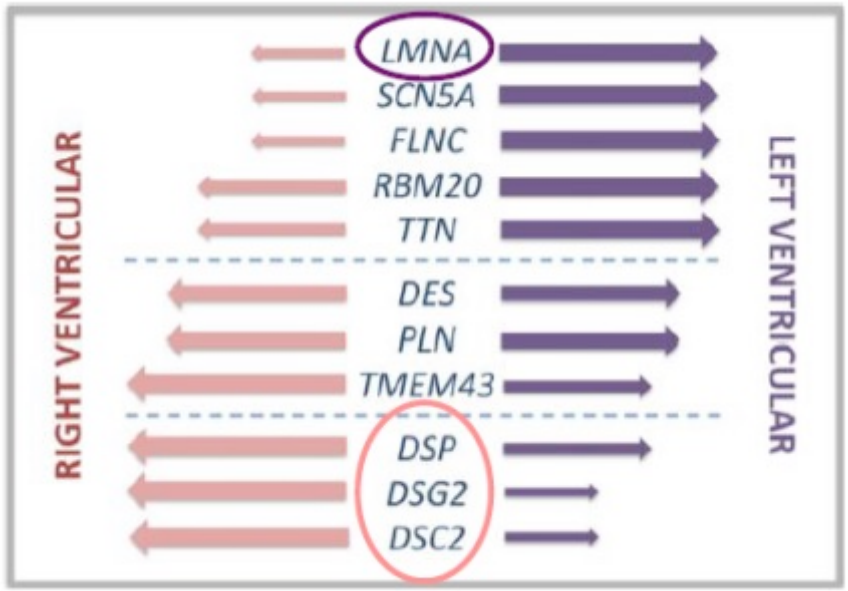
*Shown by two independent imaging modalities, ^mutation carrier or not; anti-heart autoantibody (AHA) positive or negative

Pinto YM, EHJ 2016

ARRHYTHMIC PHENOTYPES IN DILATED CARDIOMYOPATHY

Arrhythmic Genotypes in Familial Dilated Cardiomyopathy: Implications for Genetic Testing and Clinical Management

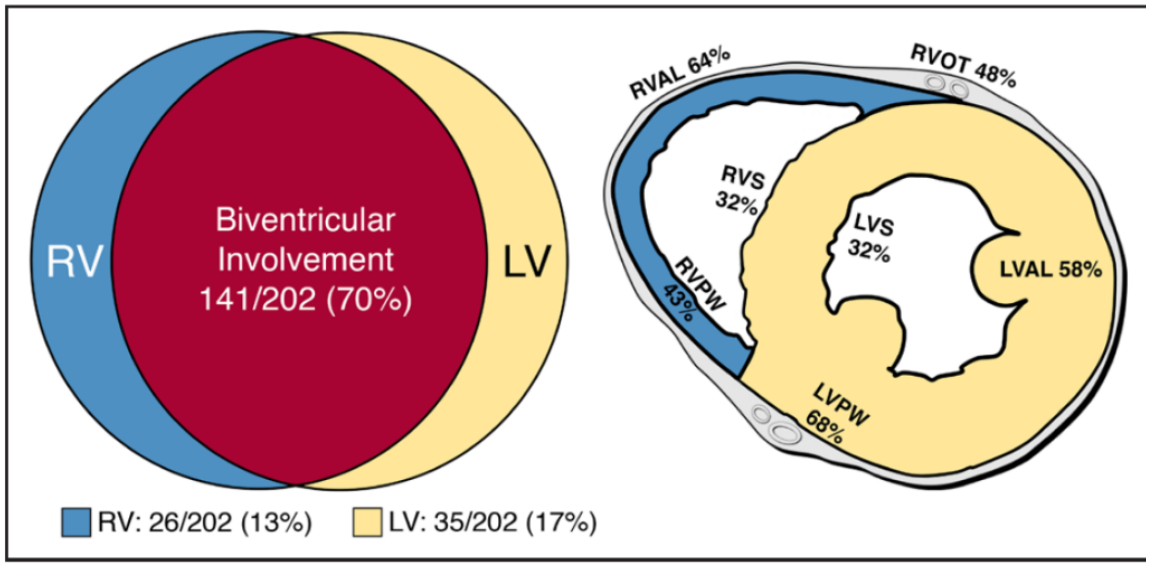


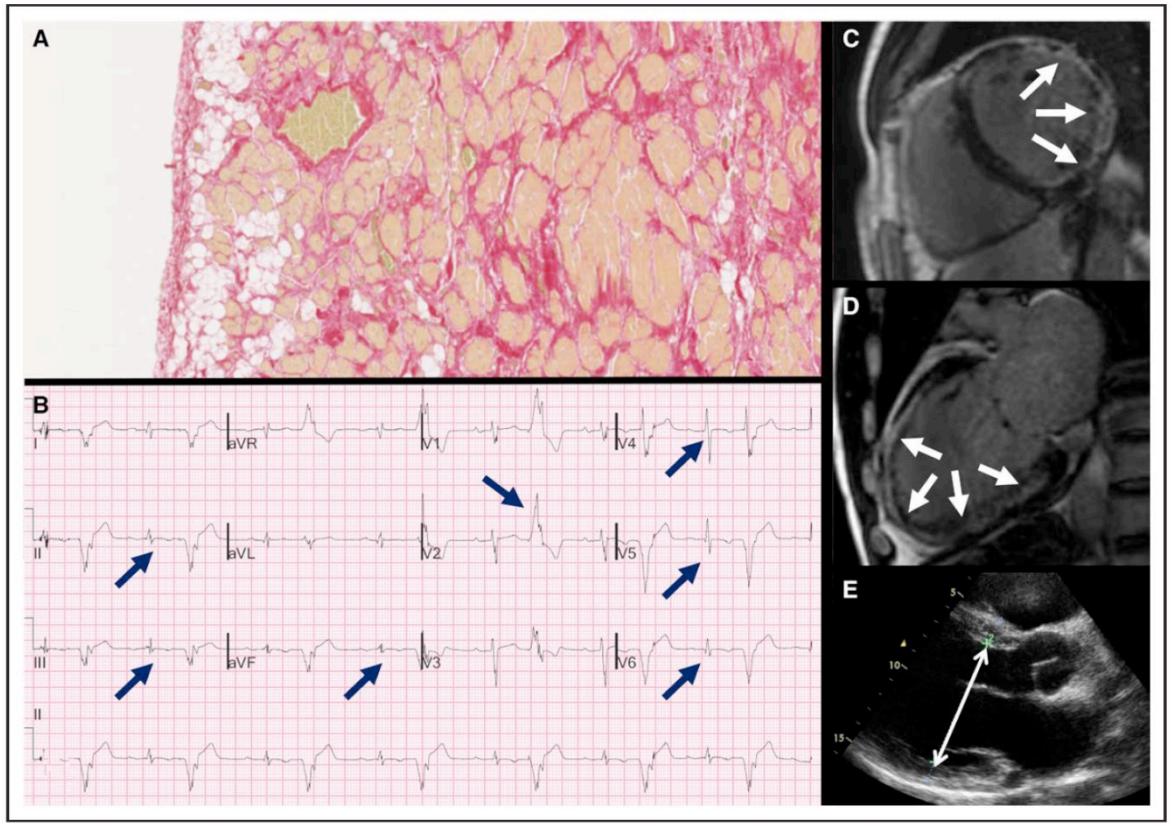


Peters S, Heart Lung Circ 2019

LEFT VENTRICULAR INVOLVEMENT IN ARRHYTHMOGENIC CARDIOMYOPATHY

Sudden Death and Left Ventricular Involvement in Arrhythmogenic Cardiomyopathy





Miles C, Circulation 2019

NEW DEFINITIONS OF ARRHYTHMOGENIC CARDIOMYOPATHY

ESC European Society of Cardiology

European Journal of Heart Failure (2019)
doi:10.1002/ejhf.1534

CONSENSUS DOCUMENT

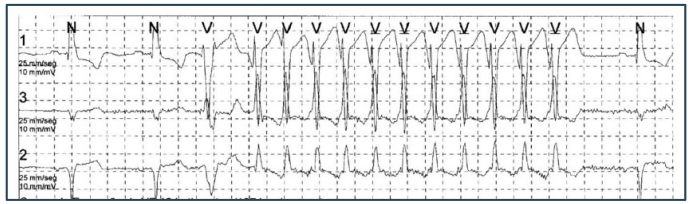
Definition and treatment of arrhythmogenic cardiomyopathy: an updated expert panel report

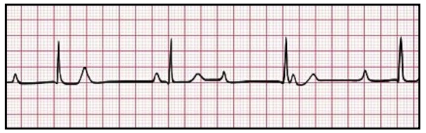
Perry M. Elliott[1]*, Aris Anastasakis[2], Angeliki Asimaki[3], Cristina Basso[4], Barbara Bauce[4], Matthew A. Brooke[5], Hugh Calkins[6], Domenico Corrado[4], Firat Duru[7], Kathleen J. Green[8], Daniel P. Judge[9], David Kelsell[5], Pier D. Lambiase[1], William J. McKenna[10], Kalliopi Pilichou[4], Alexandros Protonotarios[1], Jeffrey E. Saffitz[11], Petros Syrris[10], Hari Tandri[6], Anneline Te Riele[12], Gaetano Thiene[4], Adalena Tsatsopoulou[13], and J. Peter van Tintelen[14,15]

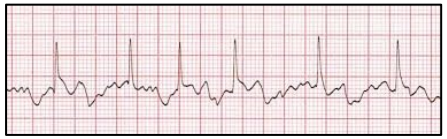
Elliott PM, EJHF 2019

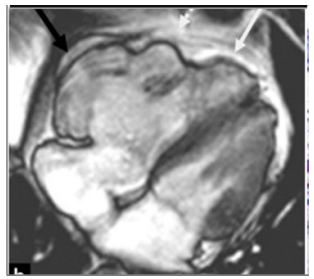
NEW DEFINITIONS OF ARRHYTHMOGENIC CARDIOMYOPATHY

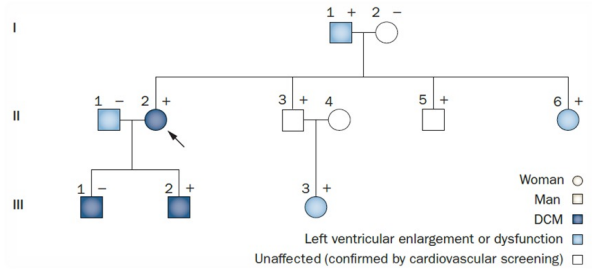
The term 'arrhythmogenic cardiomyopathy' is used to describe a family of diseases that feature structural myocardial abnormalities (identified by macro- and microscopic pathological examination besides cardiac imaging) and ventricular arrhythmia. In *Figure 1*,



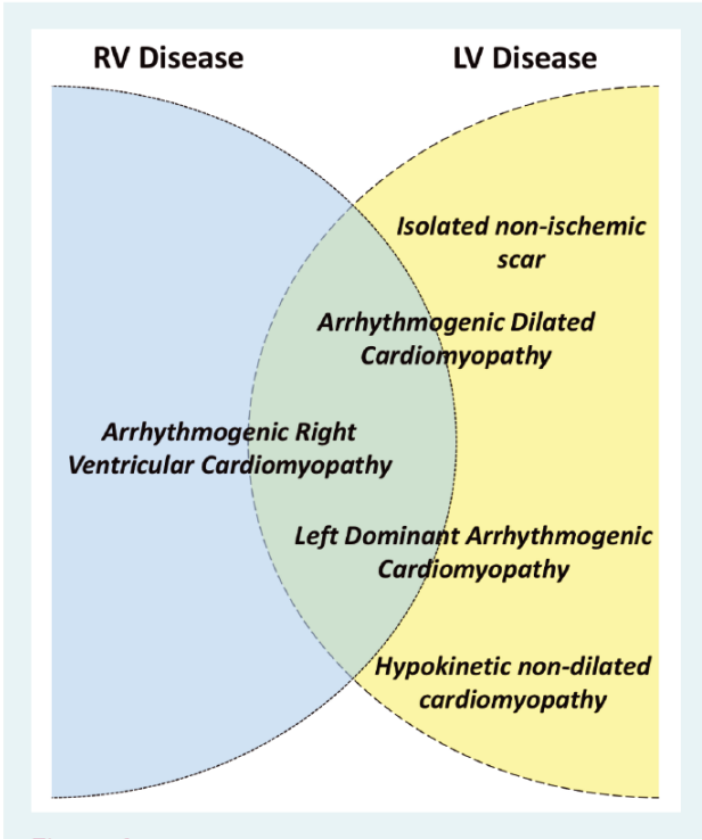








1) Arrhythmia
2) Electrical abnormalities
3) Structural abnormalities
4) Heritability
5) Phenocopy exclusion

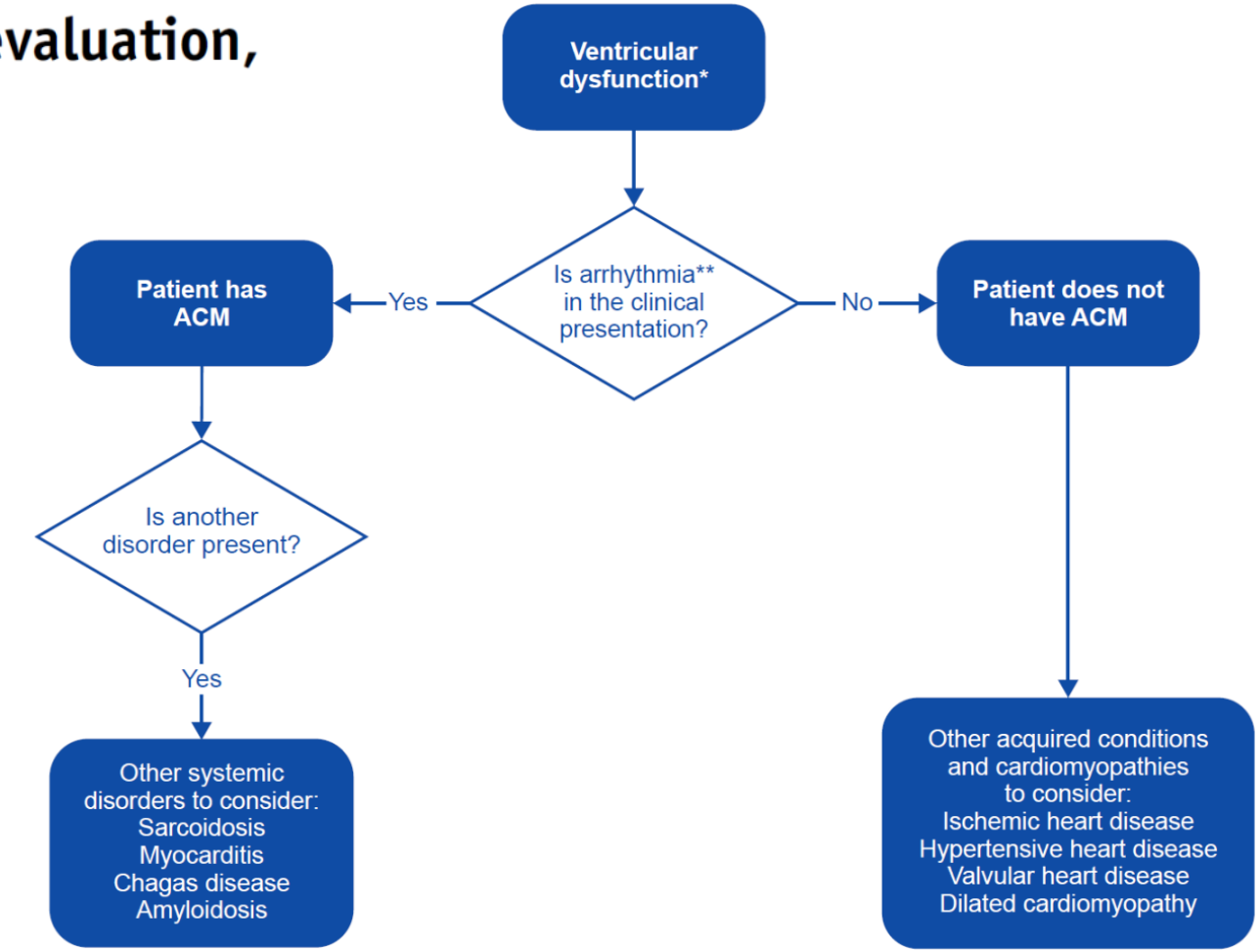


Elliott PM, EJHF 2019

NEW DEFINITIONS OF ARRHYTHMOGENIC CARDIOMYOPATHY

2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy

- Arrhythmogenic heart muscle disease **not explained by ischemia, hypertension or valvopathies**
- **Arrhythmia is the presenting feature** (AF, CD, RV or LV arrhythmias)
- **Overlapping syndromes**
- **Includes:** ARVC/ALVC, DCM, Chagas disease, Myocarditis, Sarcoidosis, Amyloidosis, LV non-compaction

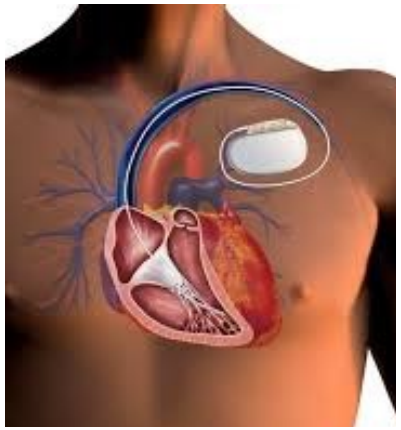


Towbin JA, Heart Rhythm 2019

ARRHYTHMIC RISK ASSESSMENT

LVEF

NYHA class

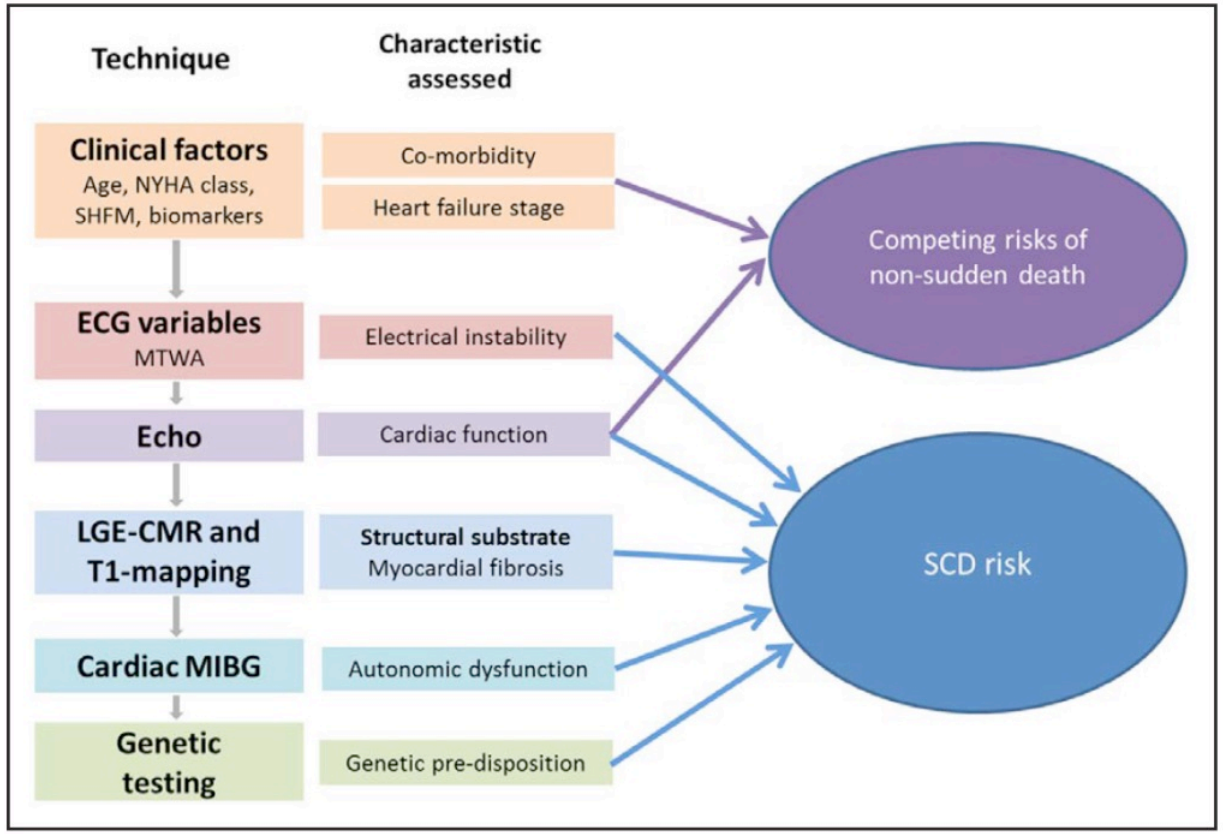


Is it enough

PERSONALIZED ARRHYTHMIC RISK ASSESSMENT

Personalizing Risk Stratification for Sudden Death in Dilated Cardiomyopathy

The Past, Present, and Future



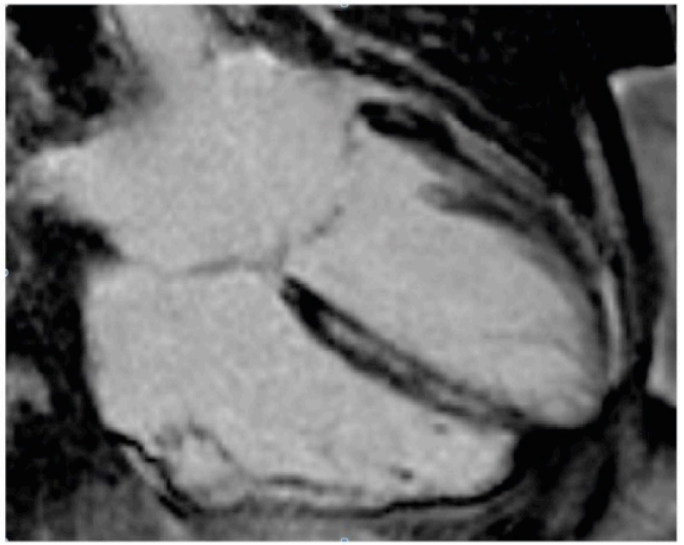
Halliday B, Circ 2017

PERSONALIZED ARRHYTHMIC RISK ASSESSMENT

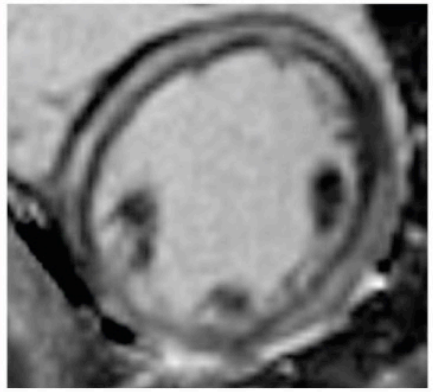
ARRHYTHMIC PREDICTORS IN DCM	
CLINICAL	
	Etiological characterization
	Personal and family history (syncope, familial history of SCD)
ECG and Holter ECG	
	Fragmented QRS
	Long QRS
	Low QRS amplitude
	Anterolateral T wave inversion
	NSVT (≥5 beats, ≥150 bpm)
	Frequent PVCs (1000/24h) and couplets (≥50/24h)
ECHOCARDIOGRAPHY	
	LVEF ≤ 35%
	Reduced GLS
CMR	
	LGE presence
	LGE extent and location (i.e. septal and free-wall)
	T1-mapping (increased T1 relaxation time)
GENETIC TESTING	
	LMNA
	FLNC, PLN, RBM20
	SCN5A
	TTN *
ELECTROPHYSIOLOGICAL PARAMETERS	Abnormal mTWA test

Cannatà A, Heart 2020

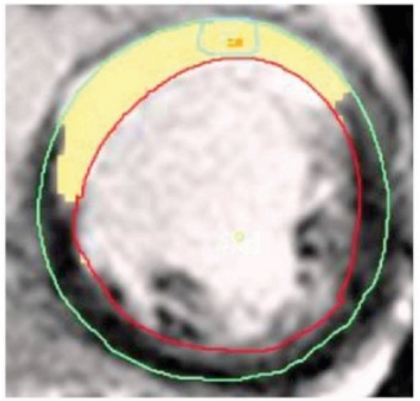
CMR – LATE GADOLINIUM ENHANCEMENT



PRESENCE / ABSENCE
Strong association with worse outcomes



LOCALIZATION
Concomitant presence of septal and free wall LGE associated with worse outcome. In the future LGE localization might provide further prognostic impact



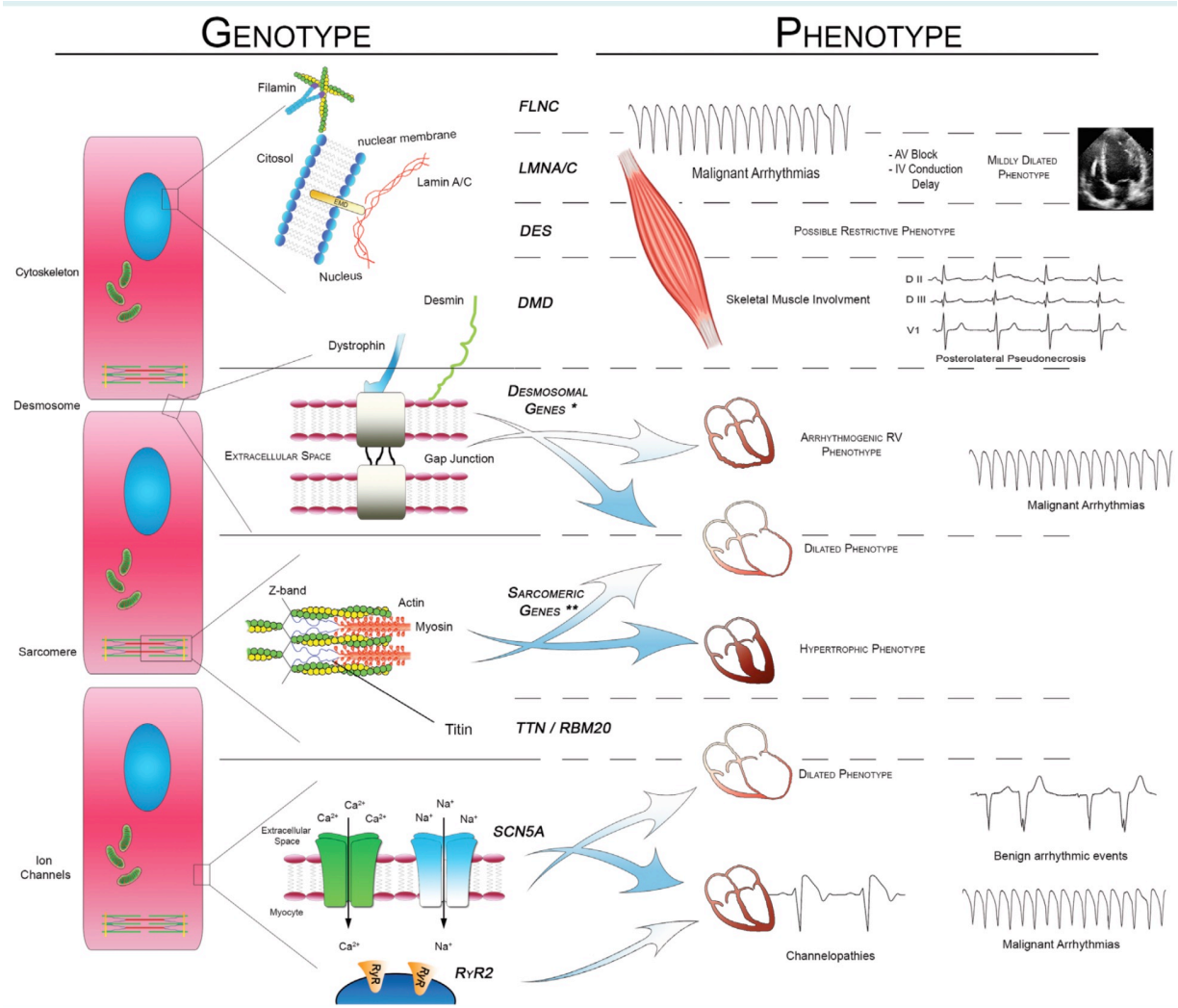
EXTENSION
Quantitative assessment might provide further prognostic impact in the future

Strong evidences in large studies and metanalyses

Conflicting evidences from smaller studies

Cannatà A, Heart 2020

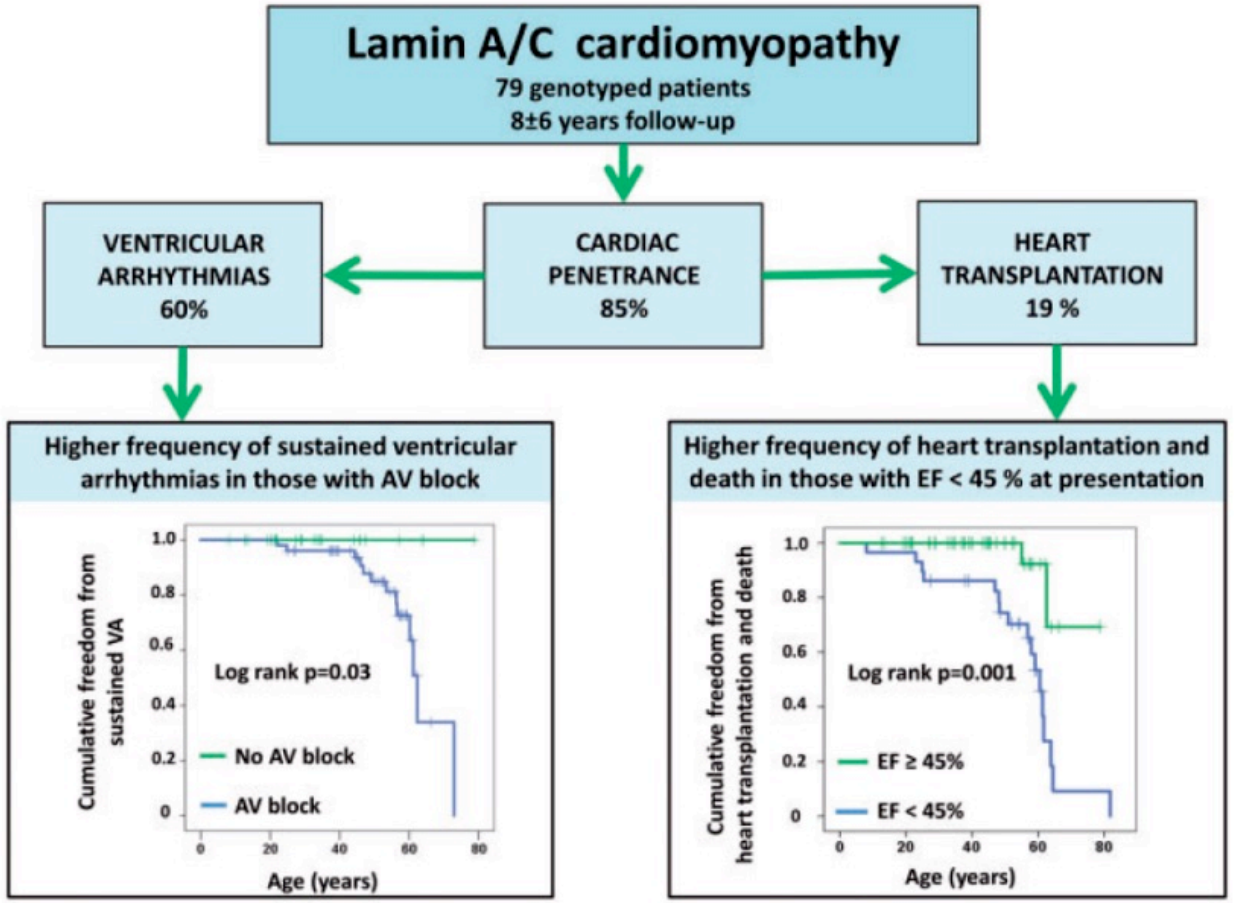
IMPORTANCE OF GENETIC PROFILING IN SUDDEN DEATH RISK STRATIFICATION



Merlo M, EJHF 2018

LMNA - Lamin A/C

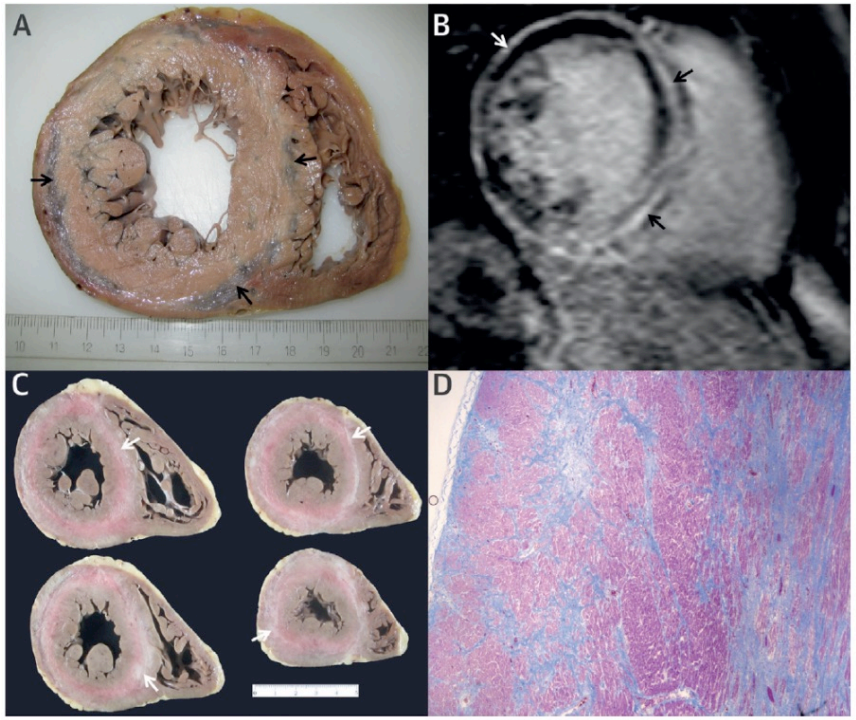
Lamin A/C cardiomyopathy: young onset, high penetrance, and frequent need for heart transplantation

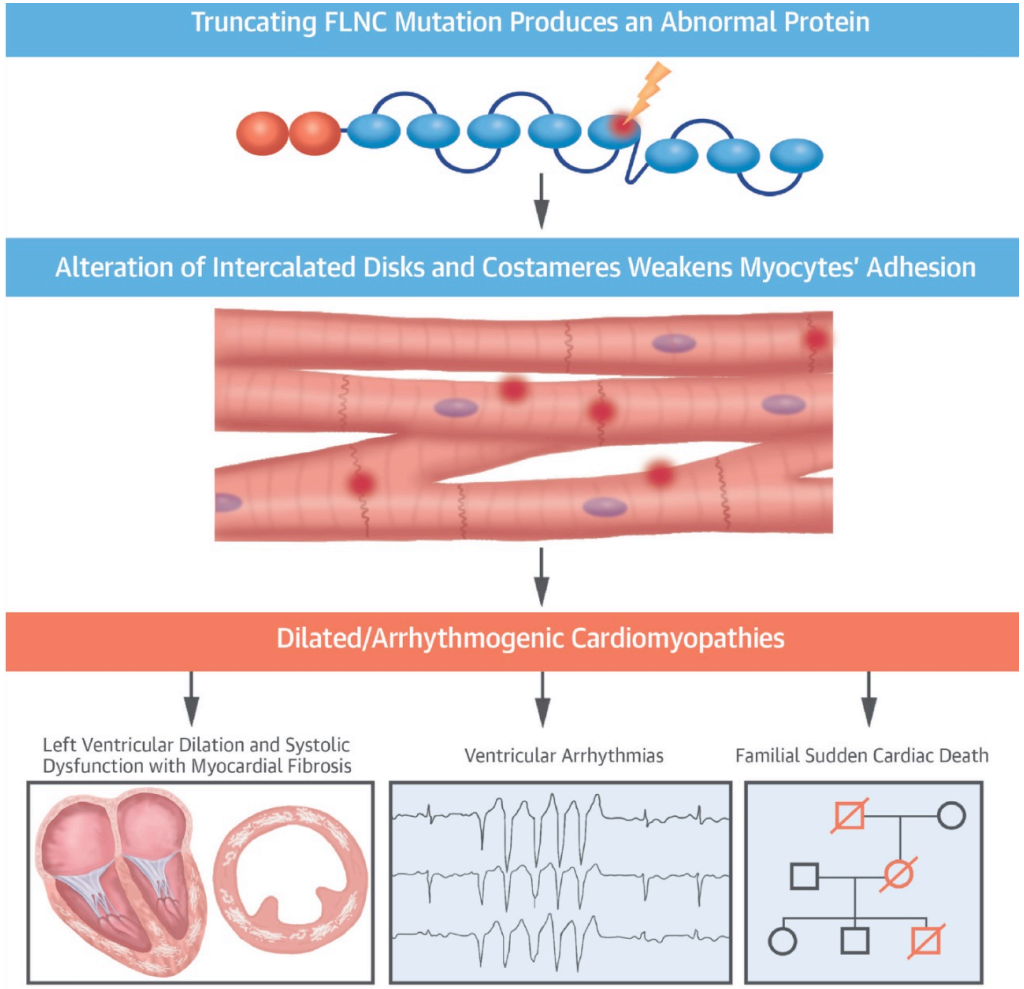


Hasselberg NE, EHJ 2018

FLNC – filamin C

Truncating *FLNC* Mutations Are Associated With High-Risk Dilated and Arrhythmogenic Cardiomyopathies



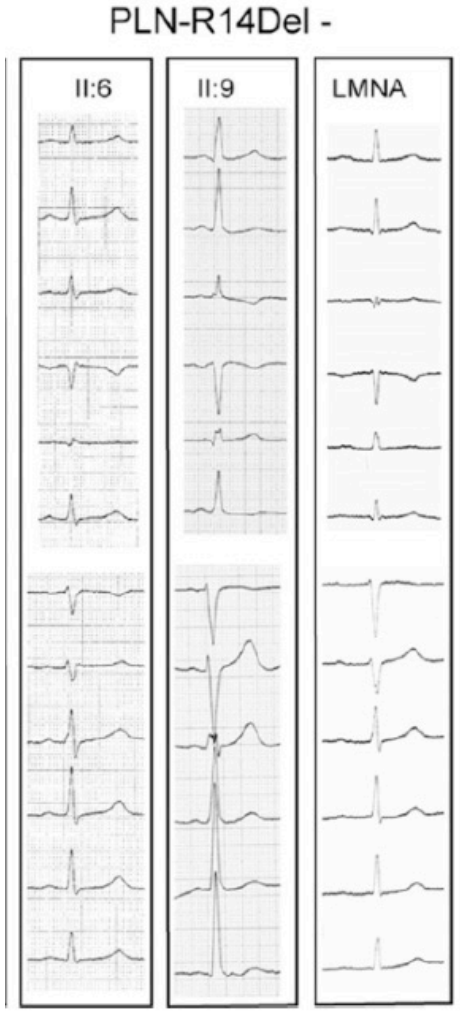


Ortiz-Genga MF, JACC 2016

PLN - phospholamban

Phospholamban R14del mutation in patients diagnosed with dilated cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy: evidence supporting the concept of arrhythmogenic cardiomyopathy

R14del mutation
(15% DCM, 12% ACM Netherlands)



We screened a cohort of 97 ARVC and 257 DCM unrelated index patients for *PLN* mutations and evaluated their clinical characteristics. *PLN* mutation R14del was identified in 12 (12 %) ARVC patients and in 39 (15 %) DCM patients. Haplotype analysis revealed a common founder, estimated to be between 575 and 825 years old. A low voltage elec-

The *PLN* R14del founder mutation is present in a substantial number of patients clinically diagnosed with DCM or ARVC. R14del+ patients diagnosed with DCM showed an arrhythmogenic phenotype, and SCD at young age can be the presenting symptom. These findings support the concept of 'arrhythmogenic cardiomyopathy'.

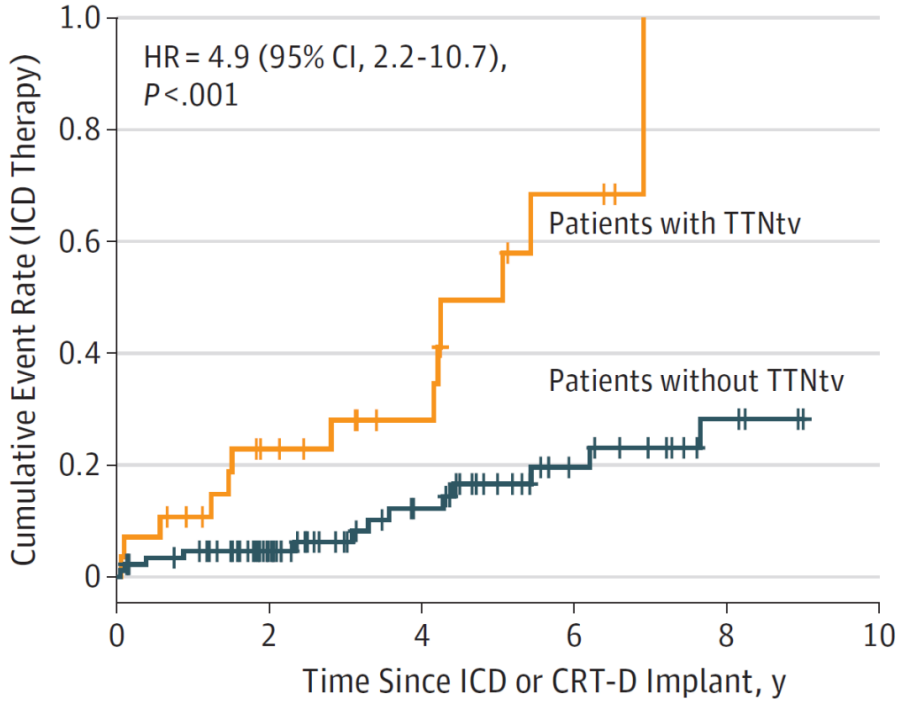
Van der Zwaag PA, Eur J Heart Fail 2012

TTN – titin

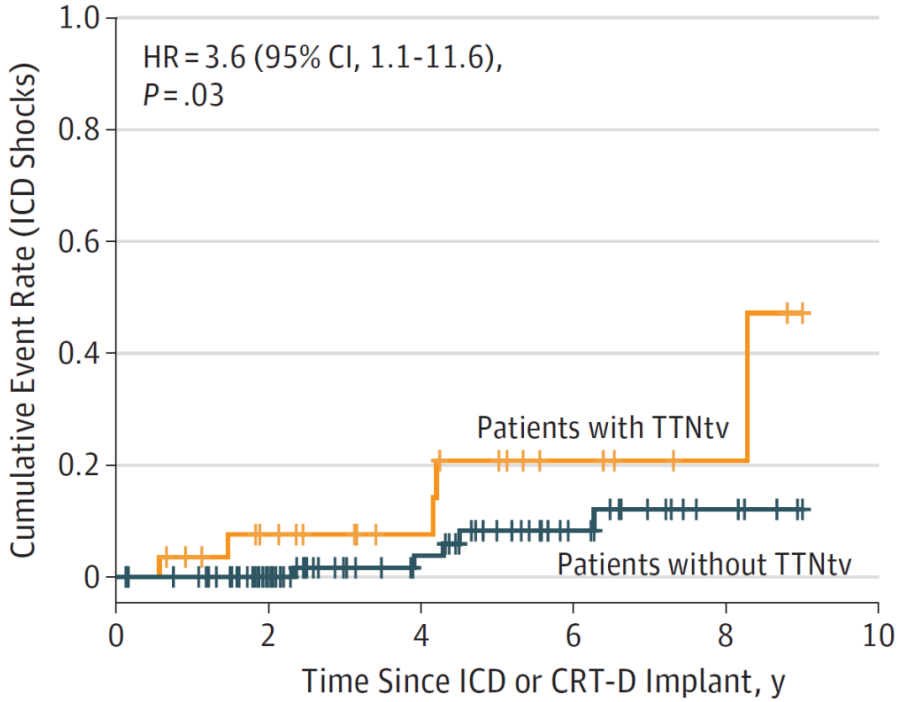
Association of Titin-Truncating Genetic Variants With Life-threatening Cardiac Arrhythmias in Patients With Dilated Cardiomyopathy and Implanted Defibrillators

The association of TTNtv with ventricular arrhythmias was independent of the presence of midwall LGE or other covariates.

A Antitachycardia pacing or shock



B Shock only

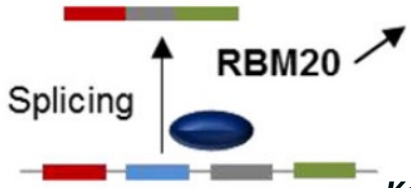


Corden B, JAMA Network Open 2019

Alexandra Sousa

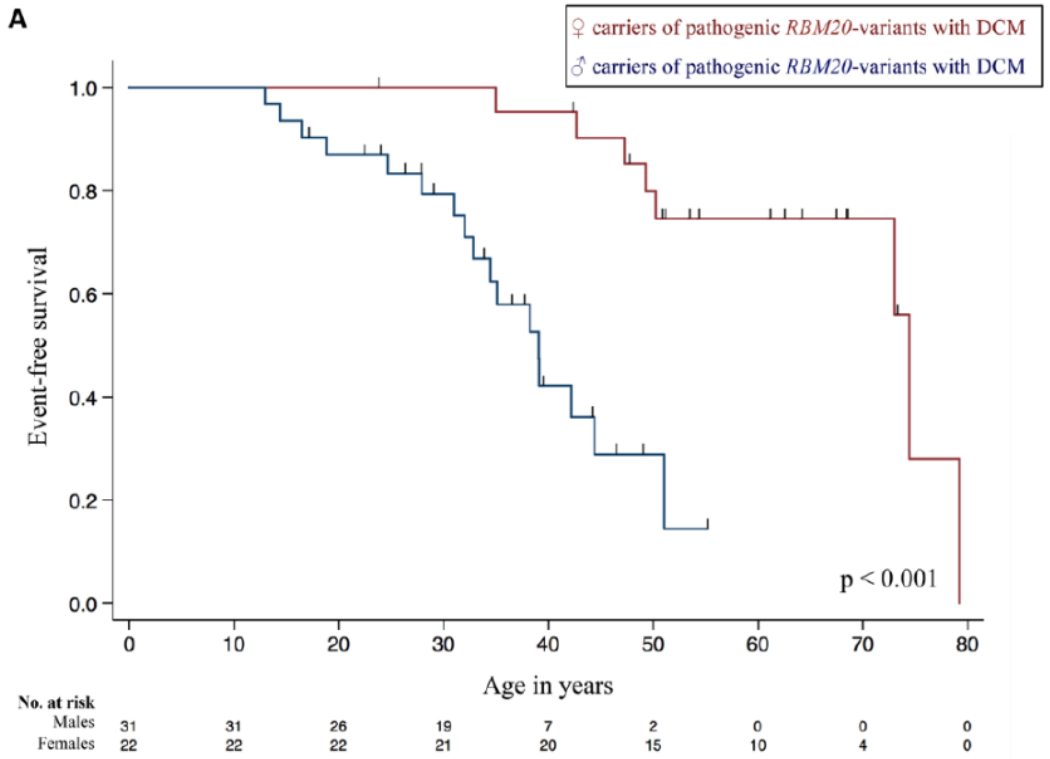
RBM20 – RNA binding motif protein 20

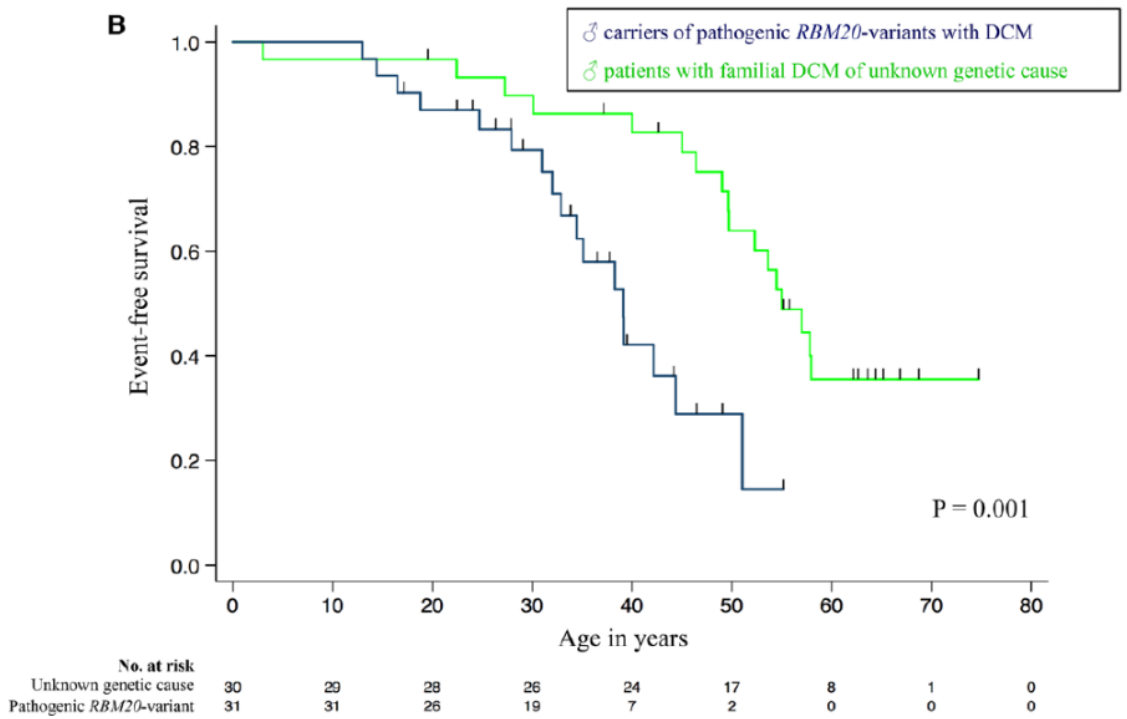
Pathogenic *RBM20*-Variants Are Associated With a Severe Disease Expression in Male Patients With Dilated Cardiomyopathy



- Frequency: 2%
- Male predominance: 59%
- Conduction disease: 30%
- HTx at younger age

Kayvanpour E, Clin Res Cardiol 2017





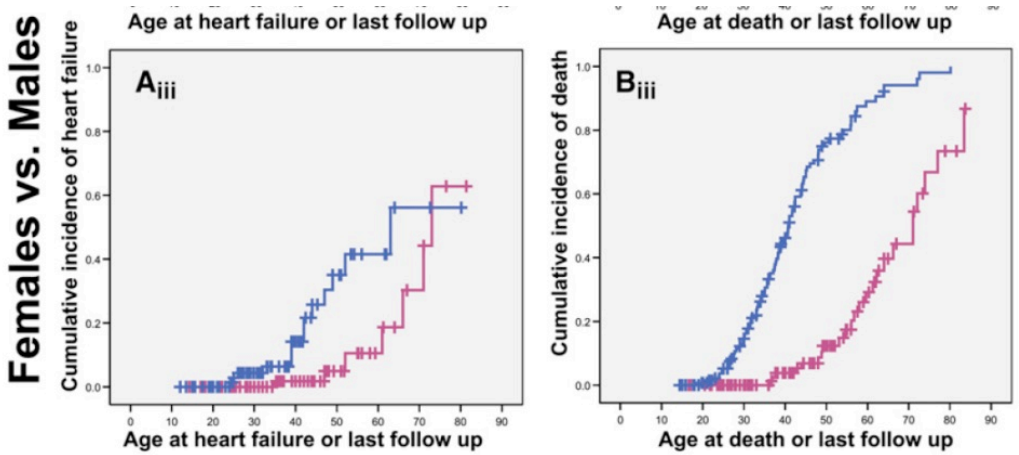
Hey TM, Circ Heart Fail 2019

Alexandra Sousa

TMEM43 – transmembrane protein 43

Arrhythmogenic Right Ventricular Cardiomyopathy Type 5 Is a Fully Penetrant, Lethal Arrhythmic Disorder Caused by a Missense Mutation in the *TMEM43* Gene

Merner ND, Am J Hum Genet 2008



***TMEM43* mutations associated with arrhythmogenic right ventricular cardiomyopathy in non-Newfoundland populations**

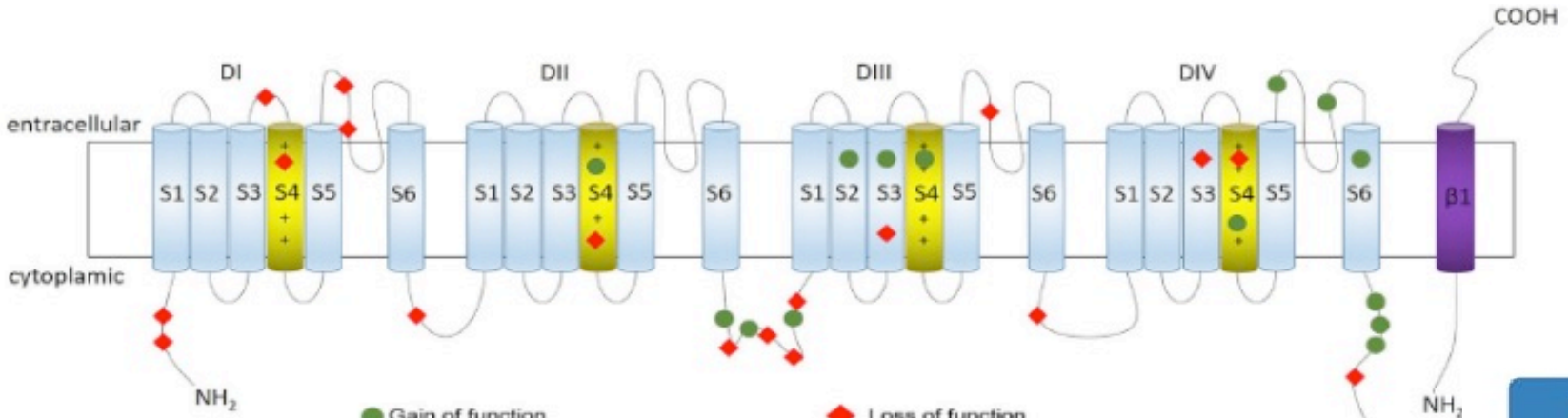
Baskin B, Hum Genet 2013

The natural history of a genetic subtype of arrhythmogenic right ventricular cardiomyopathy caused by a p.S358L mutation in TMEM43

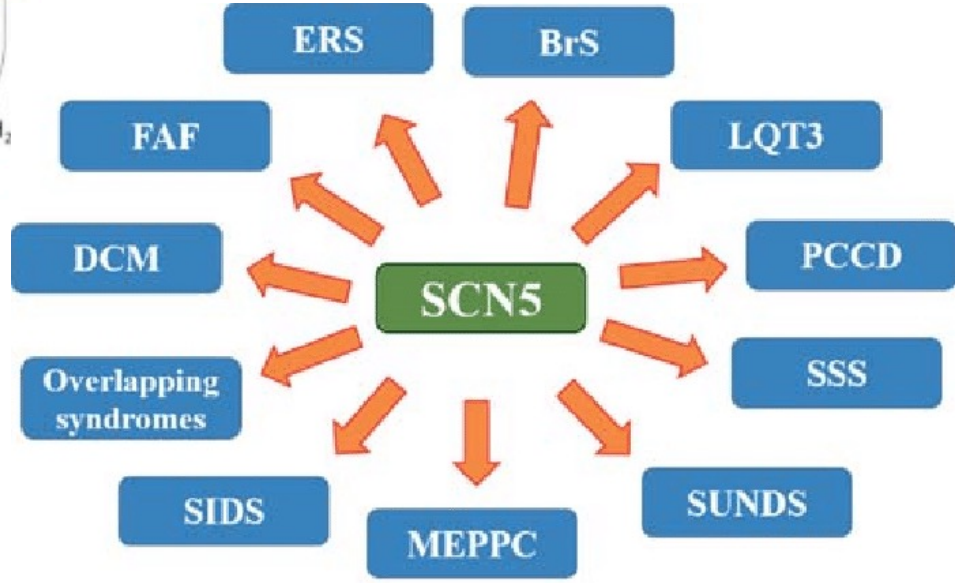
Hodgkinson KA, Clin Genet 2013

11% fullfilled DCM criteria

SCN5A – sodium channel



Gain of function		Loss of function	
R814W	DII/S4	T220I	DI/S4
F1250L	DIII/S2	L812Q	DII/S4
P1298L	DIII/S3	D1275N	DIII/S3
E1295K	DIII/S4	D1595N	DIV/S3
E1784K	DIV/S4	R1629Q	DIV/S4
I1768V	DIV/S6	P336L	D1 S3-S4 loop
T1709M	DIV S5-S6 loop	G298S	DI S5-S6 loop
F1705S	DIV S5-S6 loop	R367H	DI S5-S6 loop
A997S	DII-DIII loop	R1432G	DIII S5-S6 loop
G1084S	DII-DIII loop	T512I	DI-DII loop
E1053K	DII–III loop	R965C	DII-DIII loop
Y1795C	C-terminus	E1053K	DII-DIII loop
R1826H	C-terminus	A1180V	DII-DIII loop
H1849R	C-terminus	S1103Y	DII-DIII loop
		R1512W	DIII-DIV loop
		S1904L	C-terminus
		R43Q	N-terminus
		R34C	N-terminus

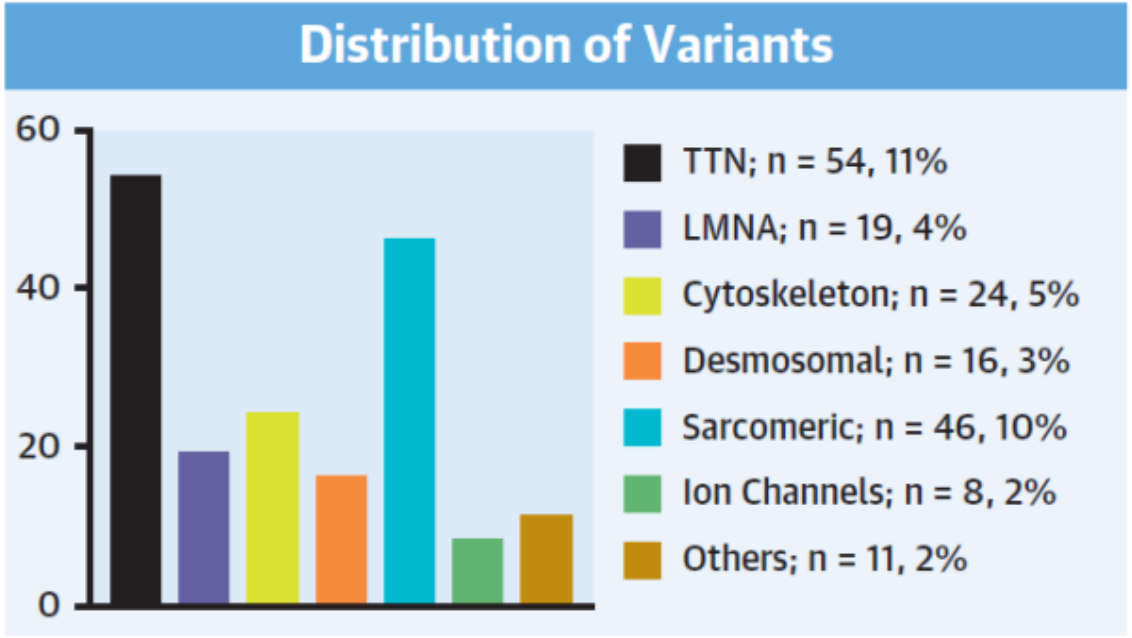


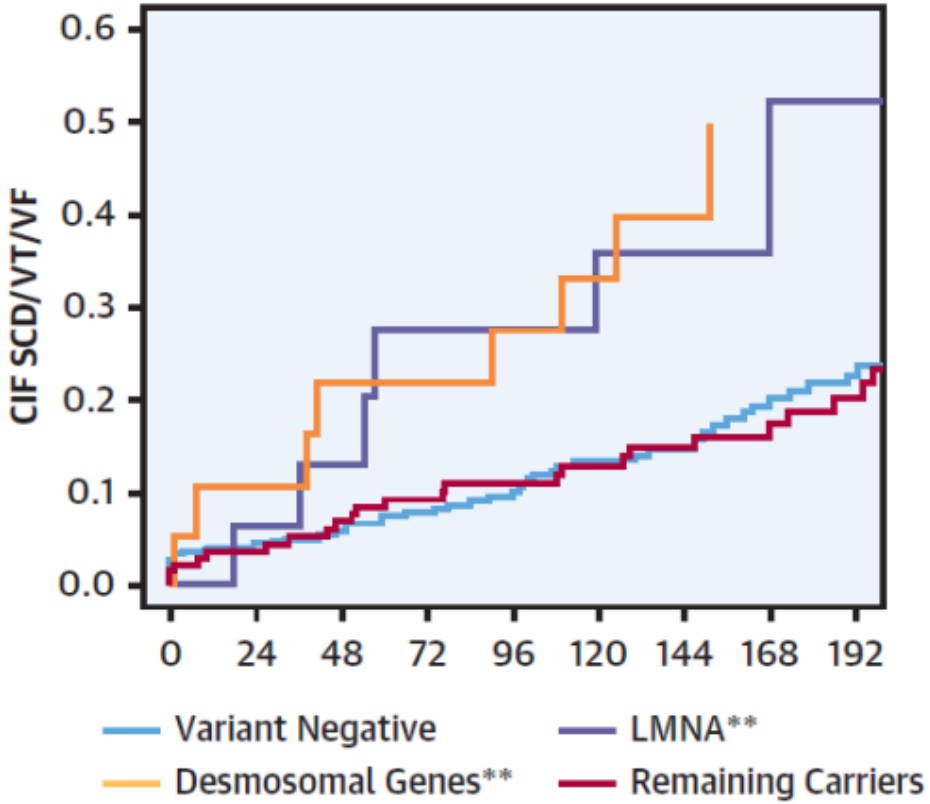
Pérez-Riera AR, J Hum Growth Dev 2016

Li W, Front Physiol 2018

Desmosomal genes – *DSP, DSC2, DSG2, PKP2*

Genetic Risk of Arrhythmic Phenotypes in Patients With Dilated Cardiomyopathy





Gigli M, JACC 2019

Alexandra Sousa

3rd PORTO MEETING 2020
September, 18th - 19th

GENETICALLY-GUIDED SUDDEN DEATH RISK STRATIFICATION

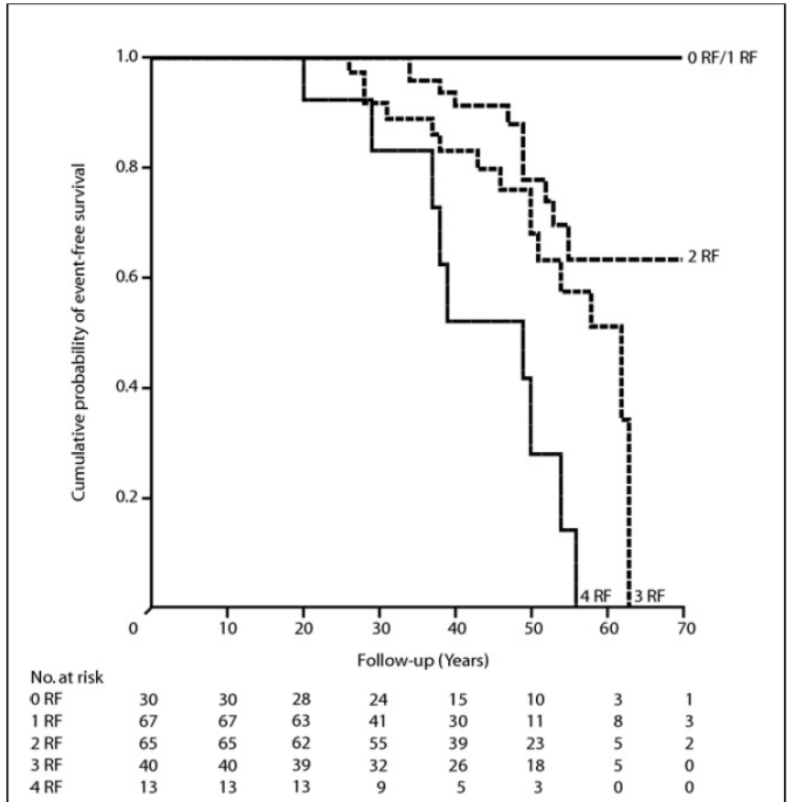
Towards precision Medicine

Alexandra Sousa

Sudden death risk stratification – *LMNA*

Risk Factors for Malignant Ventricular Arrhythmias in Lamin A/C Mutation Carriers

A European Cohort Study



An ICD should be considered in patients with DCM and a confirmed disease-causing *LMNA* mutation and clinical risk factors.[d]	IIa	B

[d]Risk factors in patients with a confirmed *LMNA* mutation: NSVT during ambulatory electrocardiogram monitoring, LVEF <45% at first evaluation, male sex and non-missense mutations (insertion, deletion, truncations or mutations affecting splicing).

Priori S, Europace 2015

In individuals with lamin A/C ACM and two or more of the following: LVEF <45%, NSVT, male sex, an ICD is reasonable.

IIa	B-NR

Towbin JA, Heart Rhythm 2019

Sudden death risk stratification – *LMNA*

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LMNA-risk VTA calculator

Risk Prediction Score for Life-Threatening Ventricular Tachyarrhythmias in Laminopathies

Sex	○ Male ○ Female	
Non-missense LMNA mutation	○ Yes ○ No	*Non-missense mutations include insertions, deletions, truncating mutations or mutations affecting splicing*
Atrio-ventricular block	○ Absent ○ 1st degree ○ High degree	*Please select the highest degree. 1st degree AV block corresponds to ≥0.20 sec PR interval and high degree AV block to type II 2nd degree or 3rd degree (and not type I 2nd degree)*
Non-sustained ventricular tachycardia	○ Yes ○ No	*NSVT corresponds to ≥3 consecutive ventricular complexes at a rate ≥120 bpm on 24-h ambulatory electrocardiographic monitoring*
Left ventricular ejection fraction	[ ] %	*Left ventricular ejection fraction measurement derived from echocardiogram*

Risk of Life-Threatening Ventricular Tachyarrhythmias at 5 years

__ %

Reset

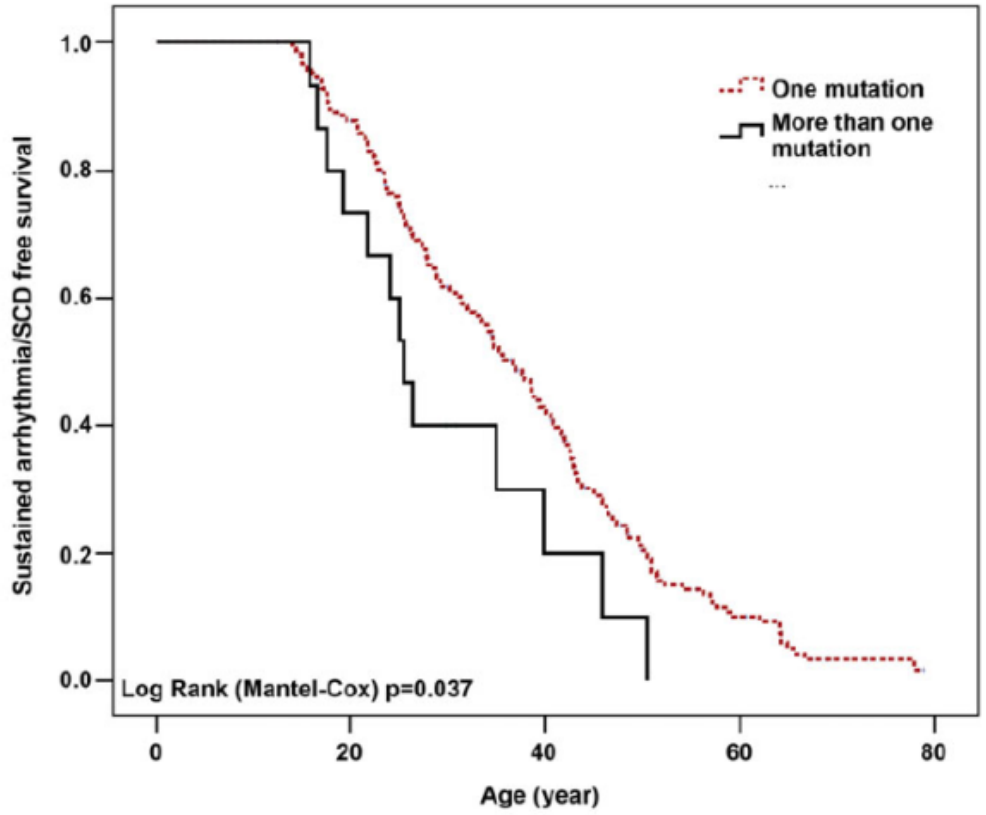
Life-Threatening Ventricular Tachyarrhythmias is defined as 1) sudden cardiac death, 2) appropriate ICD therapy, defined as a shock to terminate a VTA, or 3) other manifestations of hemodynamically unstable VTA

https://lmna-risk-vta.fr/

Alexandra Sousa

Sudden death risk stratification – desmosomal genes

Impact of genotype on clinical course in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated mutation carriers



One mutation	215	186	80	14	--
More than one mutation	15	11	2	--	--

Bhonsale A, EHJ 2015

Sudden death risk stratification – desmosomal genes

COMPLEX GENETIC *STATUS* RELATED TO WORSE PROGNOSIS

- **Compound or digenic heterozygosity** up to 25% of cases.

- **Worse clinical course**:
  - greater penetrance
  - early ventricular arrhythmias
  - higher risk of SD
  - frequent LV involvement
  - increased risk of end-stage HF

ICD implantation may be considered in patients with one or more recognized risk factors for VA in adult patients with a life expectancy >1 year following detailed clinical assessment that takes into account the lifelong risk of complications and the impact of an ICD on lifestyle, socioeconomic status and psychological health.	IIb	C

during EPS.[113,114,387,389,395,404–406] Compound or digenic heterozygosity occurs in >10% of carriers of the ARVC-causing desmosomal gene mutation and may be a risk factor for major arrhythmic events and SCD.[407] As the studies examining outcomes

Priori S, Europace 2015

Sudden death risk stratification – other genes

2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy

IIa	B-NR	In individuals with phospholamban cardiomyopathy and LVEF <45% or NSVT, an ICD is reasonable.
IIa	C-LD	In individuals with *FLNC* ACM and an LVEF <45%, an ICD is reasonable.

Towbin JA, Heart Rhythm 2019

Sudden death risk stratification – other genes

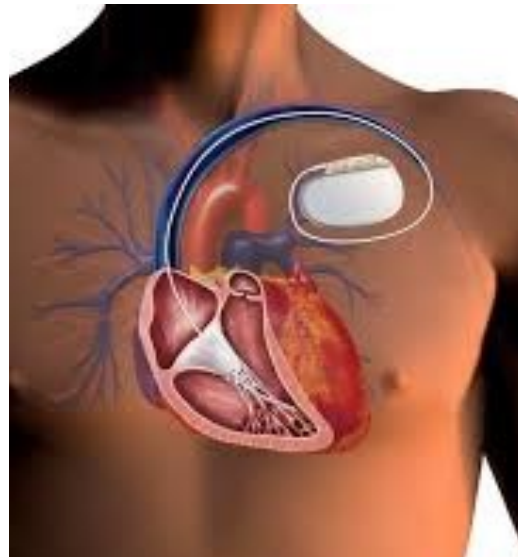
RBM20

TMEM43

SCN5A

DES

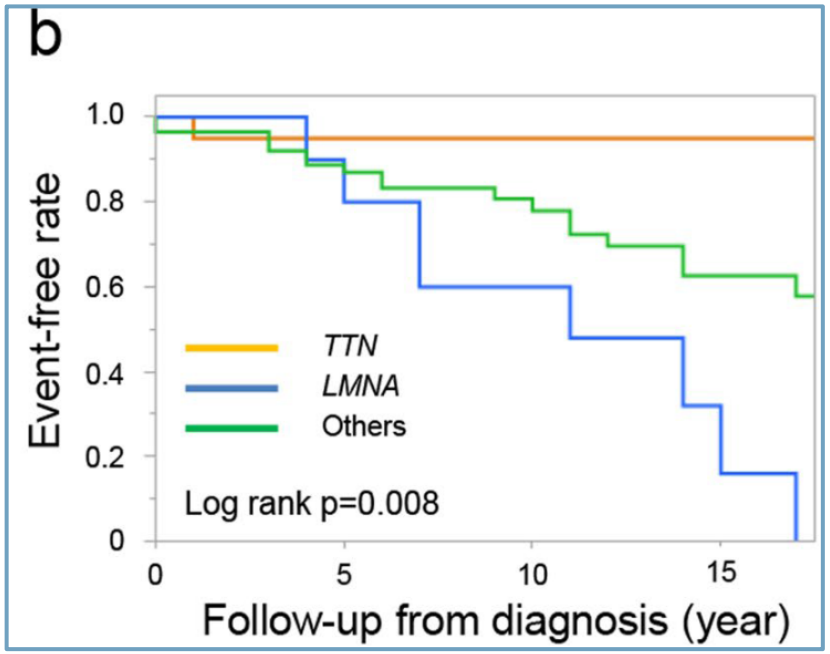
TTNtv

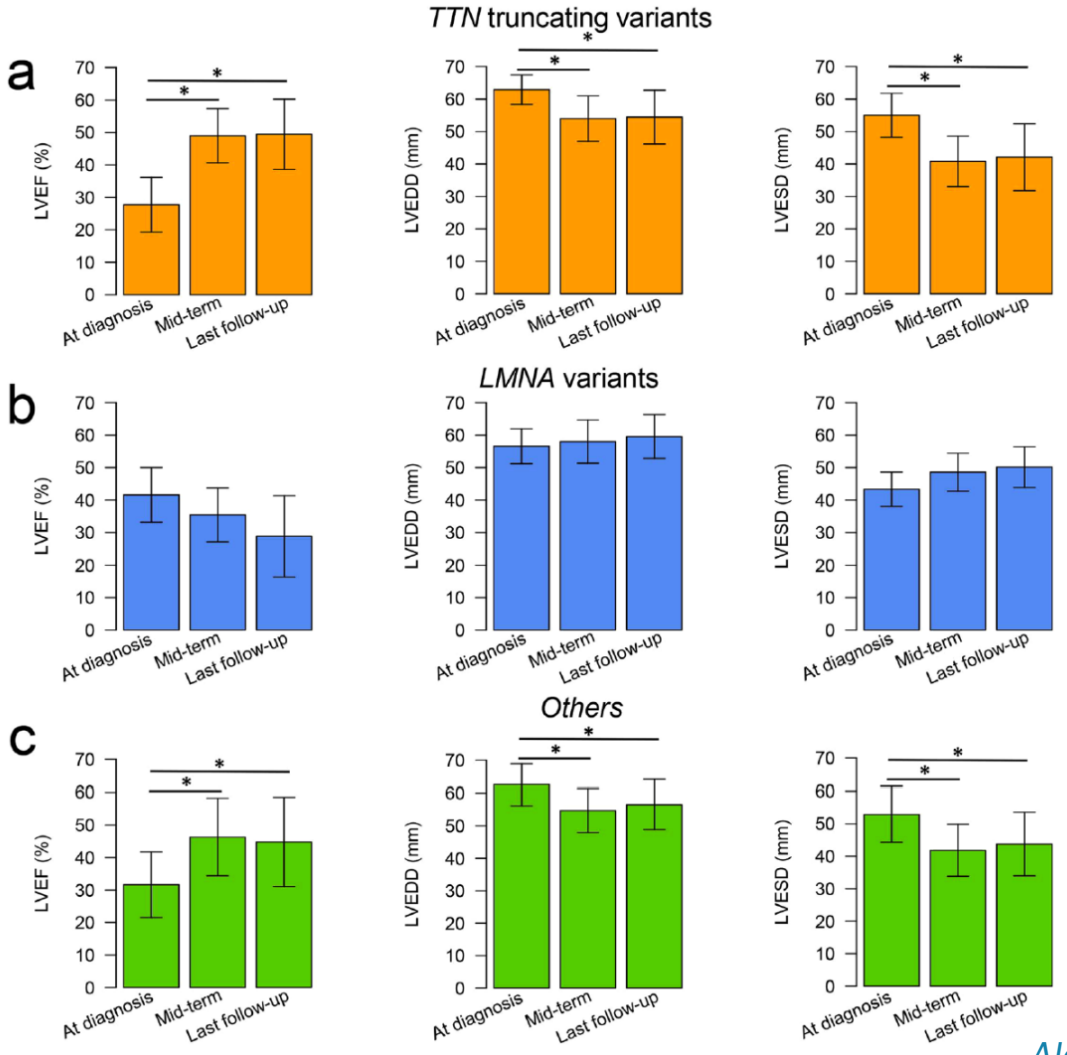


Hey TM, Circ Heart Fail 2019
Peters S, Heart Lung Circ 2019
Corden B, JAMA Network Open 2019
Bondue A, Cardiovasc Res 2018
Hodgkinson KA, Clin Genet 2013

INFLUENCE OF GENOTYPE IN REVERSE REMODELLING

Genetic basis of cardiomyopathy and the genotypes involved in prognosis and left ventricular reverse remodeling





Tobita T, Sci Rep 2018

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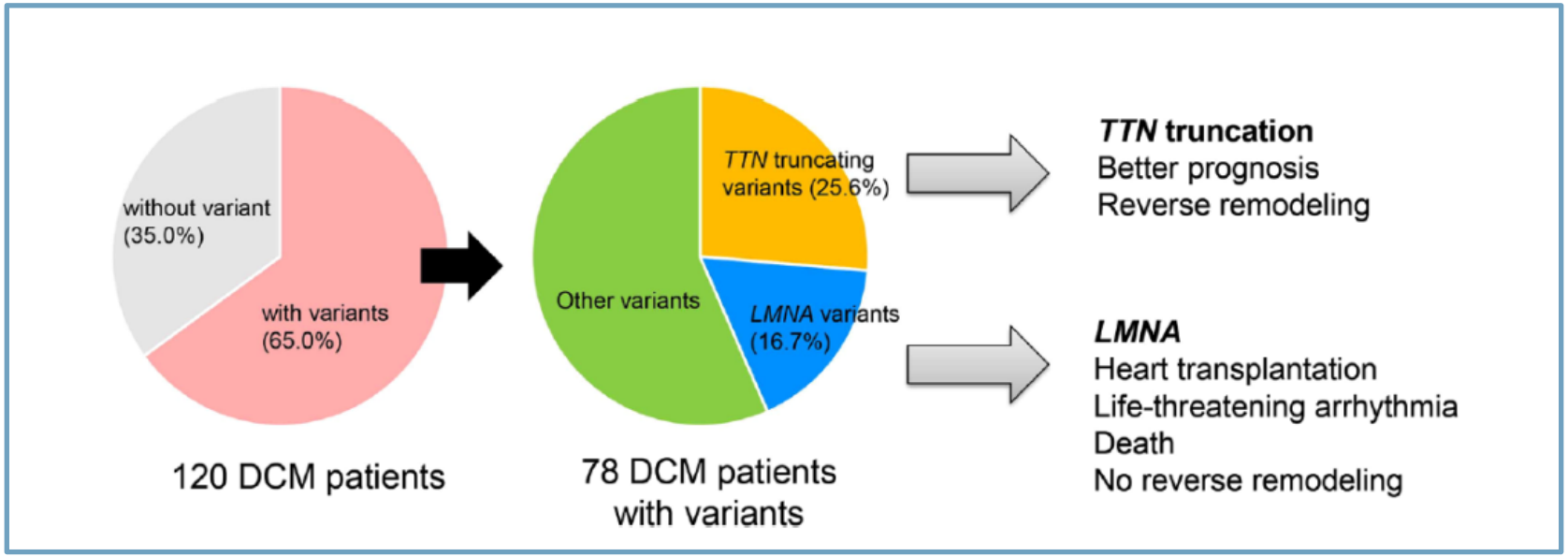
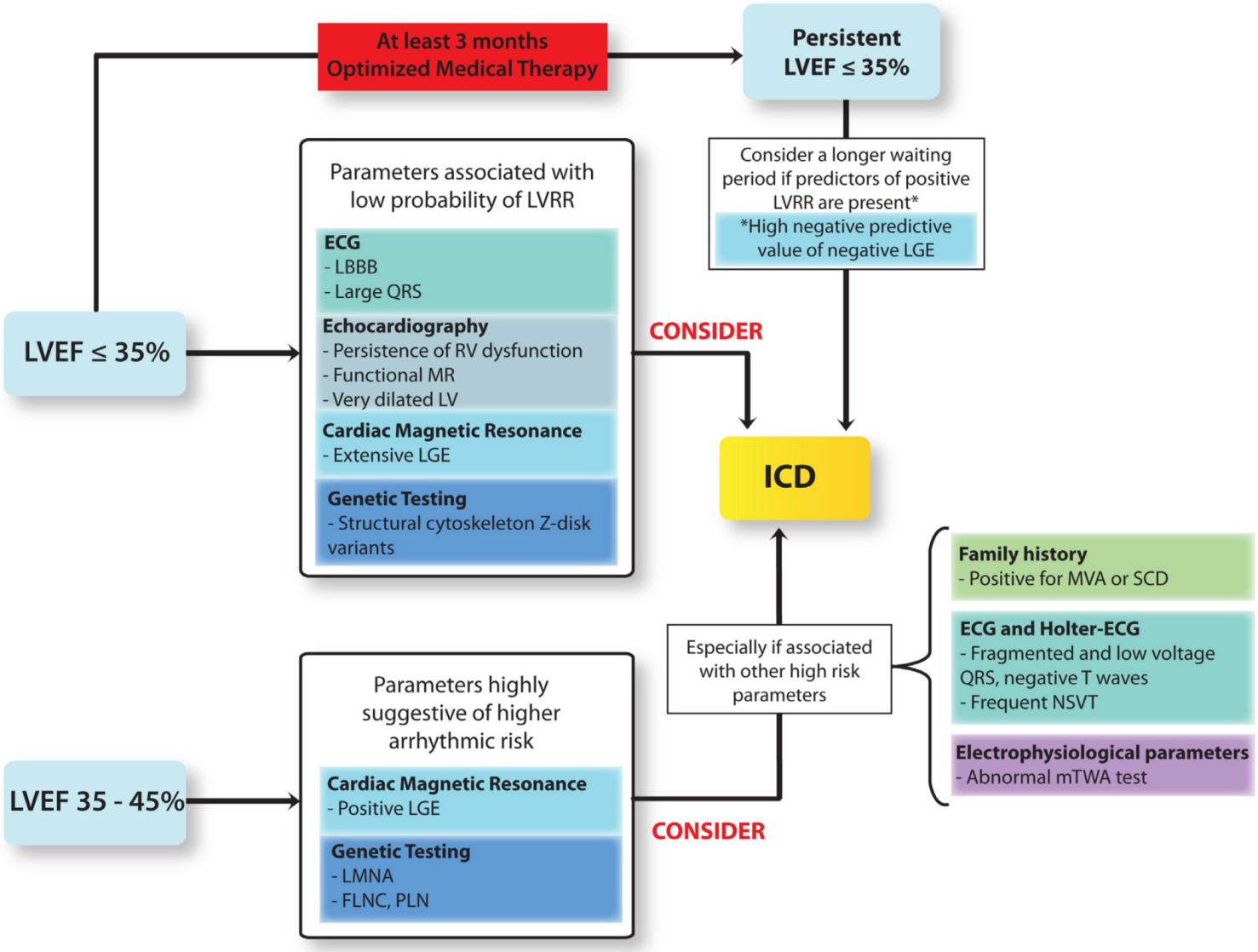


Tobita T, Sci Rep 2018

PERSONALIZED ARRHYTHMIC RISK ASSESSMENT



Cannatà A, Heart 2020

Alexandra Sousa

PERSONALIZED ARRHYTHMIC RISK ASSESSMENT

Risk Classification by Current Guidelines	+ LGE Fibrosis Assessment	+ Genetic Profiling	→ Risk Reclassification
EF ≤ 35% **High risk of SCD** **ICD is recommended**	Absence of Fibrosis on LGE	No familial DCM/SCD	**Lower risk of SCD** **Is ICD necessary?**
EF > 35% and ≤ 49% **Low risk of SCD** **ICD is NOT recommended**	Presence of Fibrosis on LGE	And/or Presence of: – Familial DCM/SCD – Gene Mutations	**Higher risk of SCD** **Is ICD useful?**

Disertori M, Frontiers in Physiol 2017

ARRHYTHMO "GENETIC" CARDIOMYOPATHIES

OVERLAPPING SYNDROMES WITH SPECIFIC SINGULARITIES DICTATED BY GENETICS

Several shared features

- Family history
- Genetic basis
- Histopathology
- Biventricular involvement
- ECG anomalies
- Arrhythmias

Personalized Medicine

- Sudden death risk stratification
- Therapeutic interventions
  - In asymptomatic pathogenic variant carriers
  - Target therapies
- Familial screening
  - Early detection of the disease
  - Management of incipient disease
  - Counselling (sports, reproductive issues...)


Vielen Dank
ありがとう
хвала
kiitos
merci
tack
dank u
הדות
謝謝
thank you
ačiū
obrigado
ευχαριστώ
dankie
شكرا

3rd PORTO MEETING 2020
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ARRHYTHMO "GENETIC" CARDIOMYOPATHIES: PERSONALIZING SUDDEN DEATH RISK STRATIFICATION

ALEXANDRA SOUSA

Faculdade de Medicina da Universidade do Porto; Grupo de Investigação CardioCare - CINTESIS; Grupo de Estudos de Biologia Celular e Genética Cardiovascular da Sociedade Portuguesa de Cardiologia; Hospital de Santa Maria Maior, E.P.E.