



Dilated Cardiomyopathy Patients The Beginning of Personalized Medicine

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Dilated Cardiomyopathy

LVEDD > 5.8 cm men

LVEDD > 5.2 cm women

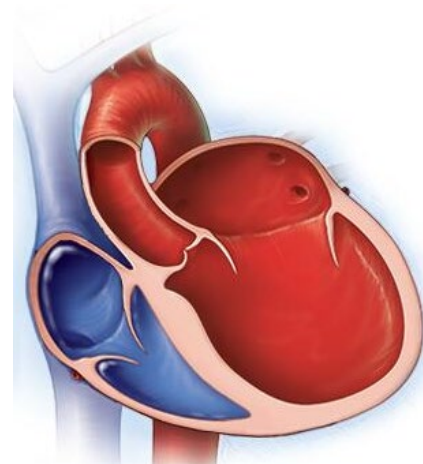
EF < 50%



Sudden Cardiac
Death



End stage heart
disease

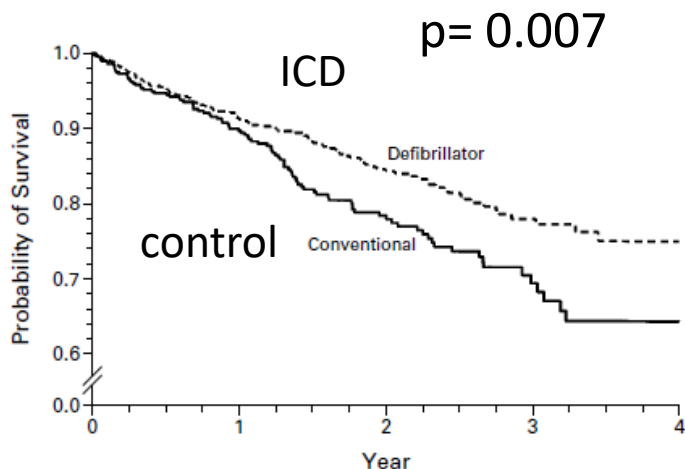




The challenge to prevent SCD in DCM

Post MI

EF < 30%

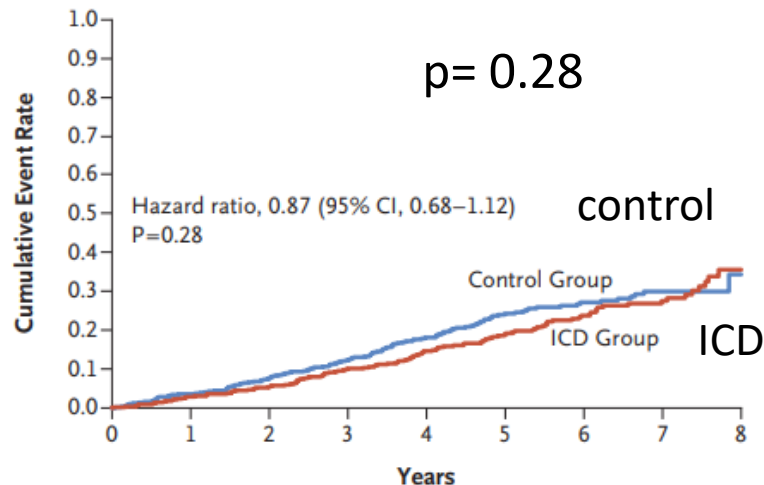


N Engl J Med, Vol. 346, March 21, 2002

DCM

EF < 35%

A Death from Any Cause

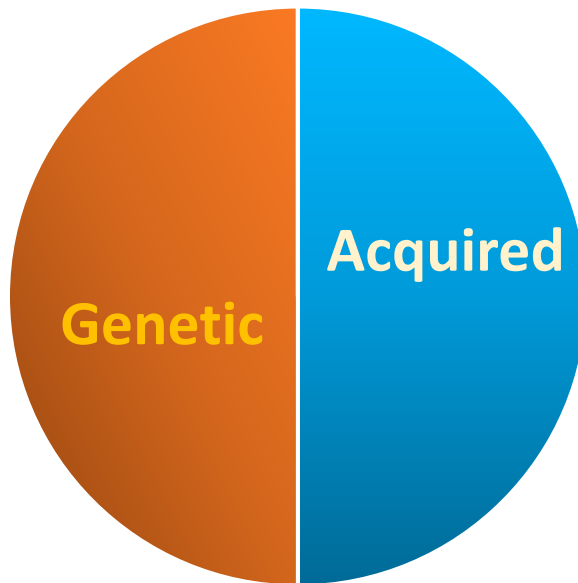


N Engl J Med 375;13 September 29, 2016



Personalized Medicine in DCM

Causes of DCM



- ▶ Infection
- ▶ Toxic/Drugs
- ▶ Autoimmune disease
- ▶ Other



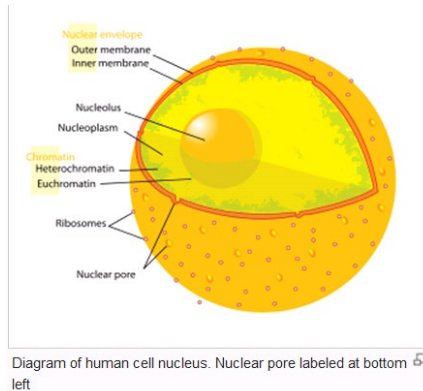
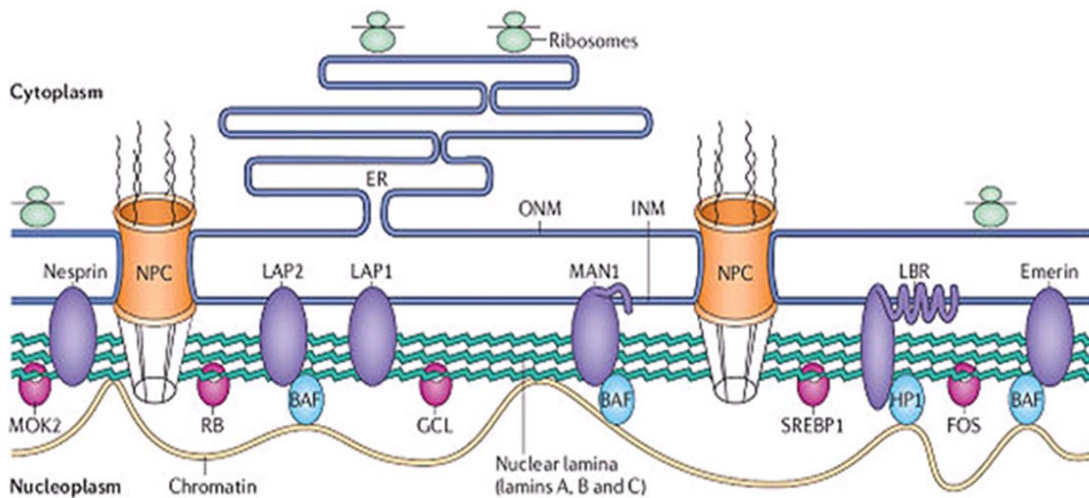
Personalized Medicine in Genetic DCM (Genes related to DCM) (146)

*ACTC1, BAG3, DES, DMD, DSP, FLNC, HCN4, **LMNA**, MYBPC3, MYH7, PKP2, PLN, RBM20, TAZ, TNNC1, TNNI3, TNNT2, TPM1, **TTN**, ABCC9, ACTA1, ACTN2, ALMS1, ALPK3, ANKRD1, ANO5, ASNA1, CAV3, CHRM2, COL7A1, CRYAB, CSRP3, DNAJC19, DOLK, DSC2, DSG2, DYSF, EMD, EYA4, FHL2, FHOD3, FKRP, FKTN, FOXD4, GAA, GATA4, GATA6, GATAD1, GLB1, GYG1, HFE, JPH2, JUP, KLF5, LAMA2, LAMA4, LAMP2, LDB3, MURC, MYBPHL, MYH6, MYL2, MYL3, MYOT, MYPN, MYZAP, NEBL, NEXN, NKX2-5, PCCA, PCCB, PLEKHM2, PPA2, PPCS, PRDM16, PSEN1, PSEN2, QRSL1, RAF1, RPL3L, RYR2, SCN5A, SDHA, SGCD, SGCG, SLC22A5, SPEG, TAZ, TBX5, TBX20, TCAP, SYNE1, SYNE2, TBX20, TCAP, TMEM43, TMEM70, TNNI3K, TRIM63, TMPO, TOR1AIP1, TTR, TXNRD2, VCL, XK, ZBTB17, AKT1, BRAF*, CASZ1, CAVIN4, CDC25B, CTF1, DNM1L*, DTNA, FBX032, FHL1, GATA5*, GLA*, GSK3B, HAND1, HAND2, IDH2*, ILK*, ISL1, KAT2B, KLHL24, KCNJ2*, KCNJ8*, JARID2, LEMD2, LMOD2, LRRC10, MEF2C, MIB1, MYLK3, NDUFB11, NNT, NONO, NKX2-5*, NRAP, NUBPL, OBSCN*, OPA3*, PDLIM3*, PDLIM5, PKD2, PPP1R13L, PRKAG2, PTPN11*, RAF1, RBM24, SGCA*, SGCB*, SURF1, TLL2, TMOD1, TUFM.*

Yield of Genetic Test 50%



גן LMNA מקודד לחלבון lamin A/C





Clinical characteristics of patients with LMNA mutation (n=299)

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Age at presentation (years)	All patients n=299
Age (years)	31.2
Male/female/unknown sex	163/119/17
No of unaffected carriers	27
Dysrhythmias	181
Sinus bradycardia	14 (5%)
Atrioventricular block	135 (45%)
Atrial fibrillation	47 (16%)
Arrhythmia, unspecified	67
Pacemaker implanted	84 (28%)
Left ventricular end diastolic diameter (mm)	52
Fractional shortening	28%
Left ventricular dilation	77
Systolic dysfunction	93 (31%)
Heart failure	78



Mode of death of patients with LMNA mutation (n=299)

All patients n=299	
No of patients died	76 (25%)
Age at death (years)	46
Sudden death	35 (46%)
With pacemaker	16
Without pacemaker	19
Due to heart failure	9
With pacemaker	3
Without pacemaker	6
Unclassified death	32
With pacemaker	13
Without pacemaker	19



Implantable cardioverter-defibrillators in laminA/C mutation carriers with cardiac conduction disorders

47 patients , LMNA mutation carrier

ICD

Bradycardia
Pacemaker
PR > 240 msec + CLBBB or NSVT

21 patients with ICD

11 (52%) appropriate shock
(9 with EF > 45%)
0 SCD

26 patients without ICD

3 heart transplantation
1 stroke
1 cancer
1 SCD



Univariate analysis for predictive factors of malignant ventricular arrhythmia



Variable	Hazard ratio (95% confidence interval)	p
Age	1.02 (0.96-1.09)	0.45
Sex: male	1.18 (0.38-3.65)	.78
Non-missense mutation	2.56 (0.56-11.63)	.22
Prior syncope	1.74 (0.58-5.23)	.32
Family history of sudden death	1.09 (0.32-3.75)	.89
Family history of syncope	1.04 (0.30-3.52)	.96
Atrial fibrillation or flutter	1.17 (0.38-3.63)	.79
Significant conductive disorders	5.20 (1.14-23.53)	.03
Nonsustained ventricular tachycardia	0.45 (0.15-1.42)	.17
Left ventricular ejection fraction	1.00 (0.95-1.05)	.87
Left ventricular ejection fraction <45%	0.64 (0.08-4.91)	.67
Left ventricular end-diastolic diameter	1.10 (0.99-1.21)	.06
Left ventricular end-diastolic diameter > 56 mm	1.33 (0.44-4.08)	.62
Beta-blockers	2.14 (0.65-7.01)	.21
ACE inhibitors/angiotensin receptor blockers	1.14 (0.35-3.71)	.83
Amiodarone	2.41 (0.78-6.42)	.19
Class 1 antiarrhythmic drugs	0.66 (0.09-5.17)	.70
Vitamin K antagonists	2.94 (0.90-8.80)	.09
Isolated skeletal muscular involvement	0.26 (0.06-1.20)	.08
Dilated cardiomyopathy phenotype	1.94 (0.65-5.78)	.24



Kaplan Meier estimate of the probability of survival free of malignant ventricular arrhythmia

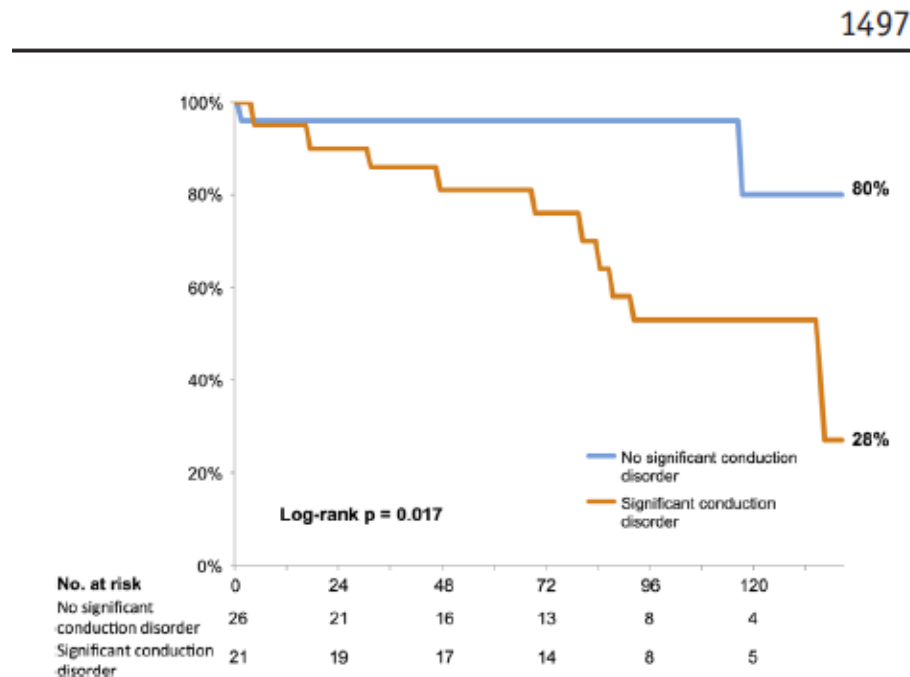




Table 2

**Malignant Ventricular Arrhythmias
and End-Stage Heart Failure (N = 269)**

Malignant ventricular arrhythmias

Cardiopulmonary resuscitation (n = 262)*	11 (4)
Appropriate ICD treatment (n = 117)*	28 (24)
Sudden cardiac death	14 (5)

End-stage heart failure

Heart transplantation	36 (13)
Death during or after heart transplantation (n = 36)*	6 (17)
Death due to end-stage heart failure	21 (8)
Other causes of death	4 (1)

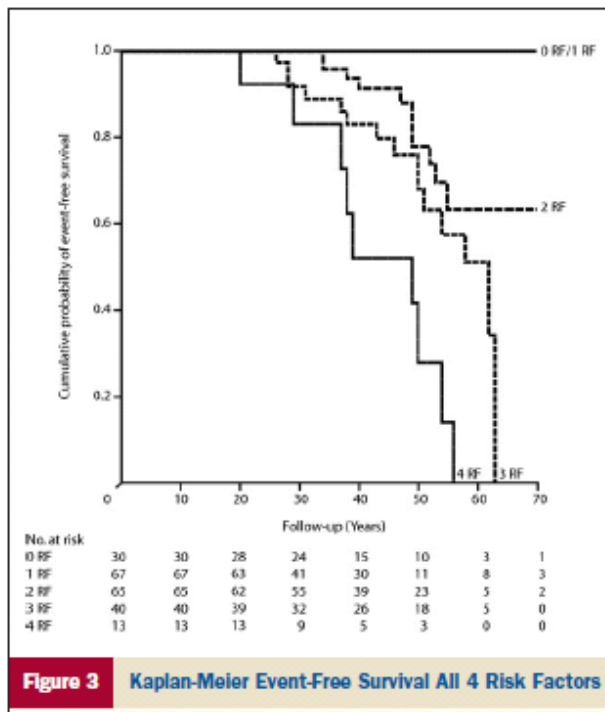
Values are n (%). *Number of persons for whom there were available data.

ICD – implantable cardioverter-defibrillator.



Kaplan Meier event free survival all 4 risk factors

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NSVT on holter
EF < 45%
Male
Non missense mutation



An ICD should be considered in patients with DCM and a confirmed disease-causing LMNA mutation and clinical risk factors

**II
a**

B

71

NSVT on holter

EF < 45%

Male

Non missense mutation



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

Table 2. Associations Between Predictors and Survival in the Derivation Sample

Characteristics	Model			
	Full Multiple Variable	P Value	Final	P Value
Age at baseline, y	0.99 (0.97–1.01)	0.200		
Men	1.80 (1.1–2.95)	0.029	1.67 (1.1–2.55)	0.017
Nonmissense <i>LMNA</i> mutation	1.78 (1.12–2.85)	0.043	1.76 (1.16–2.65)	0.007
AV block				
First degree*	2.74 (1.34–5.61)	0.002	2.35 (1.34–4.12)	0.003
>First degree†	3.51 (1.5–8.19)	0.001	2.86 (1.54–5.31)	<0.001
Atrial arrhythmia	1.19 (0.71–1.99)	0.524		
Nonsustained VT	2.25 (1.34–3.79)	0.002	2.15 (1.36–3.41)	0.001
Left ventricular ejection fraction, %	0.98 (0.96–1.00)	<0.001	0.98 (0.97–1)	0.017

Values are hazard ratios (95% CIs). The hazard ratios were pooled over the 25 imputed data sets. Hazards ratios in the final model are shrunk by the calibration slope (0.894). AV indicates atrioventricular; and VT, ventricular tachycardia.

*First degree only vs no AV block.

†All degrees vs no AV block.



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

48.6 %

[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



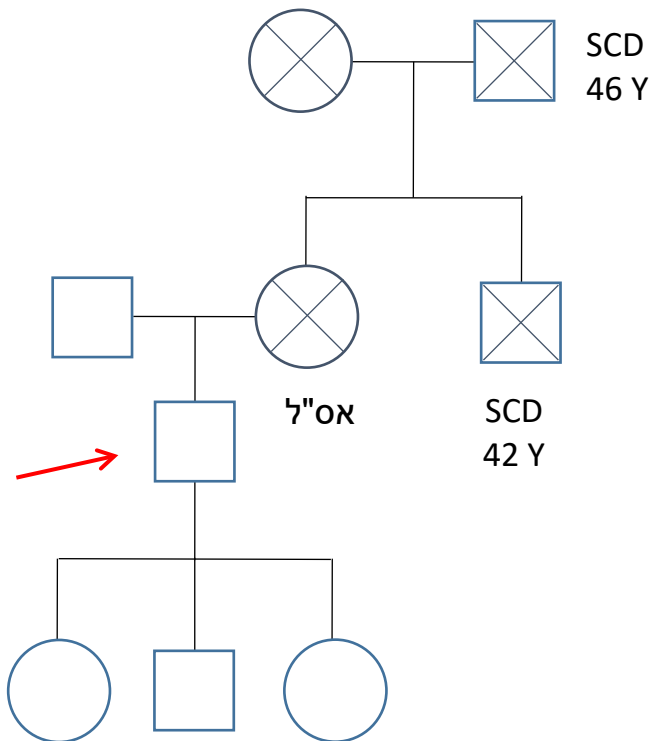
ICD implantation should be considered in DCM / HNDCM patients with a pathogenic mutation in *LMNA* gene, if the estimated 5-year risk of life-threatening VA is $\geq 10\%^c$ and in the presence of NSVT or LVEF $< 50\%$ or AV conduction delay. [80.652.653](#)

IIa

B

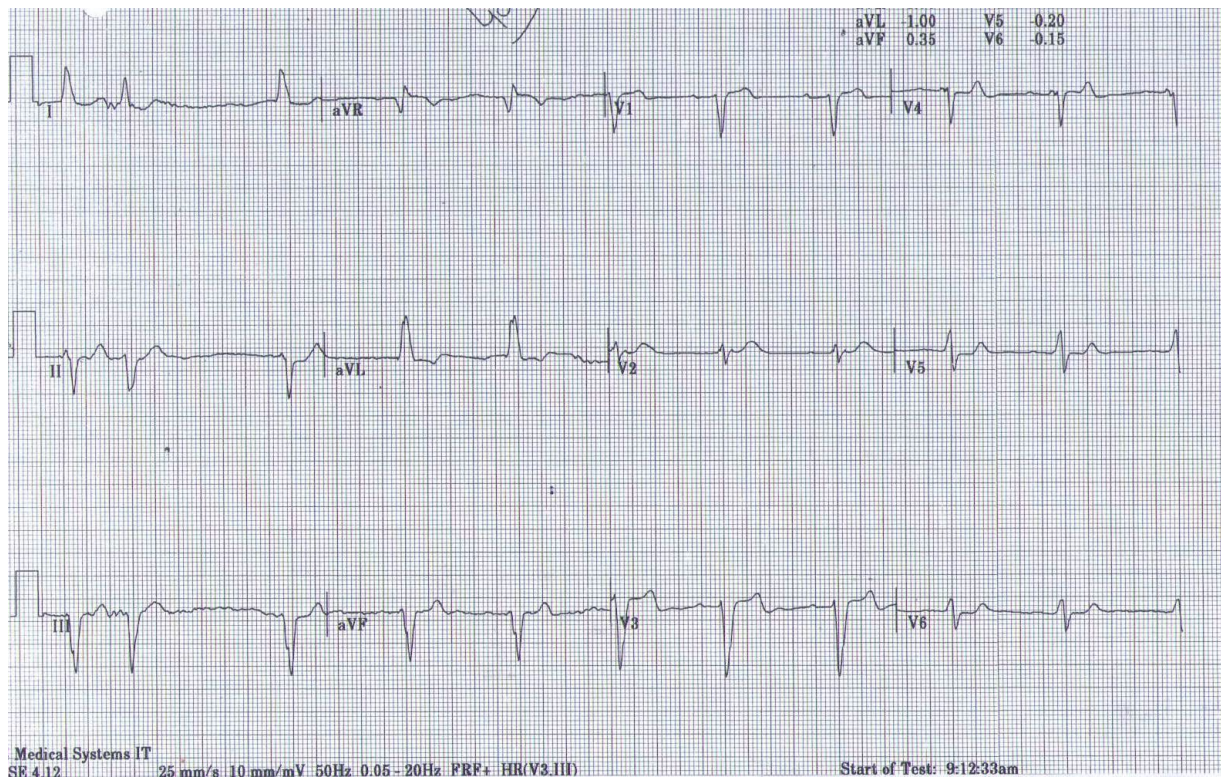


הצגת מקרה - עץ משפחה





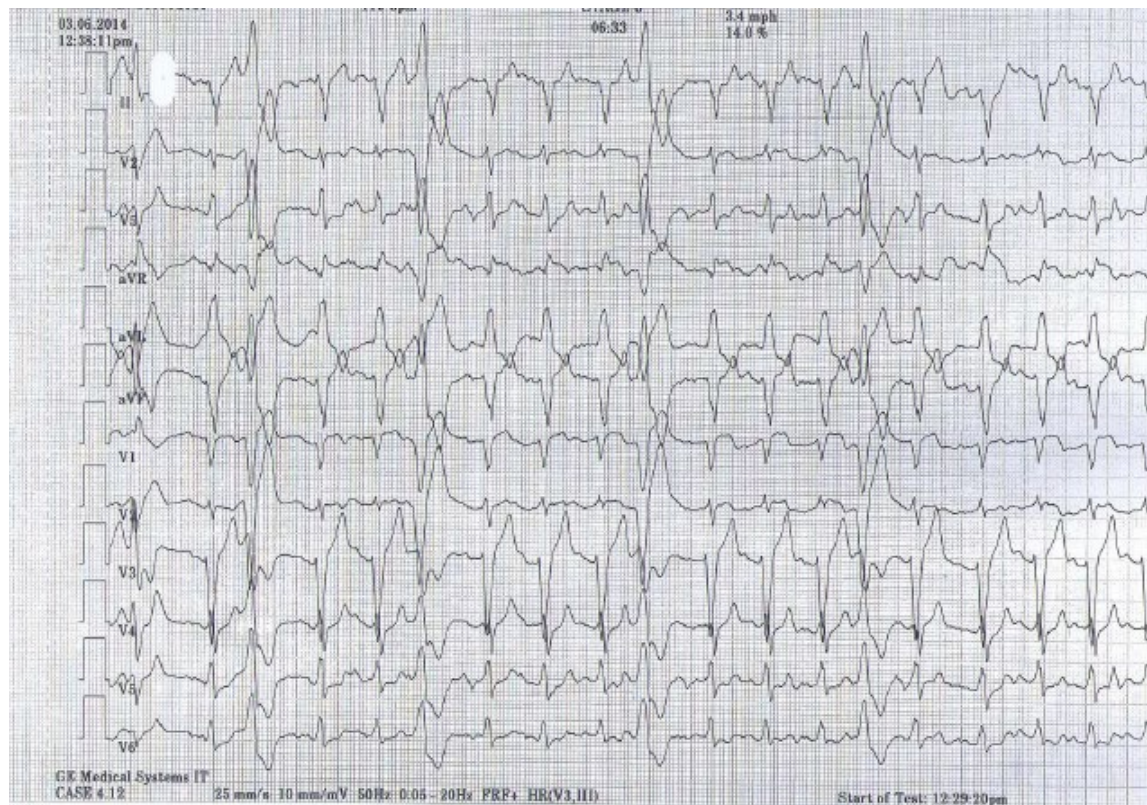
הצגת מקרה - תרשים א.ק.ג





הצגת מקרה - מבחן מאמץ

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הצגת מקרה - מבחן מאמץ

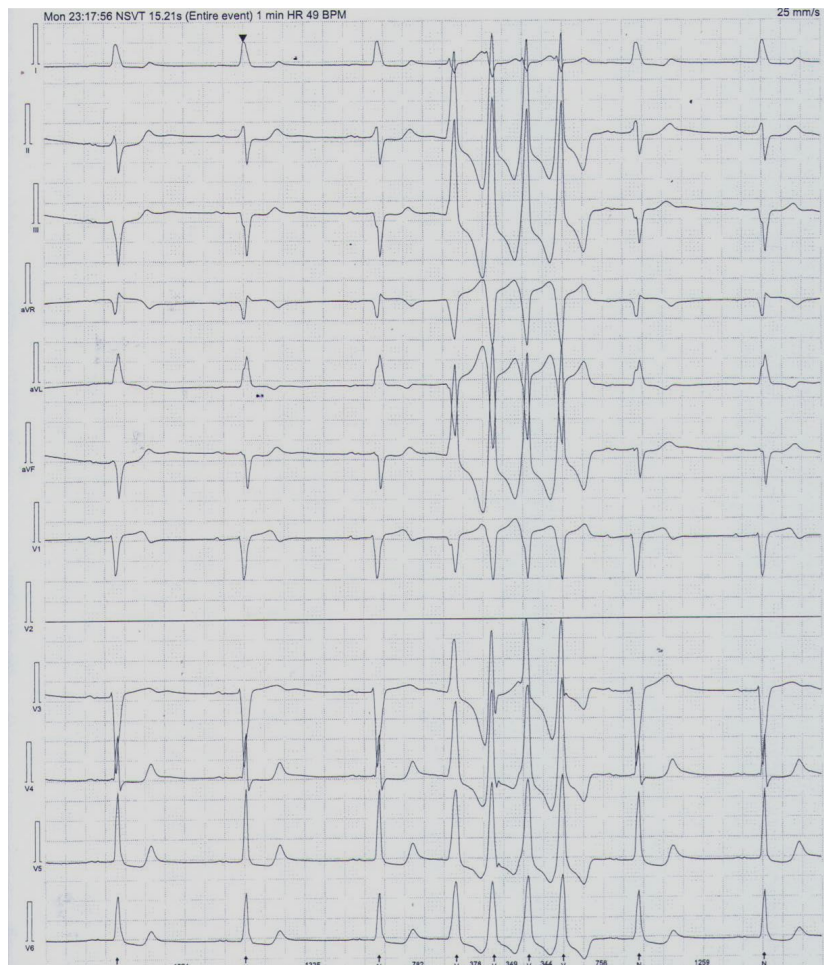
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רמב"ם

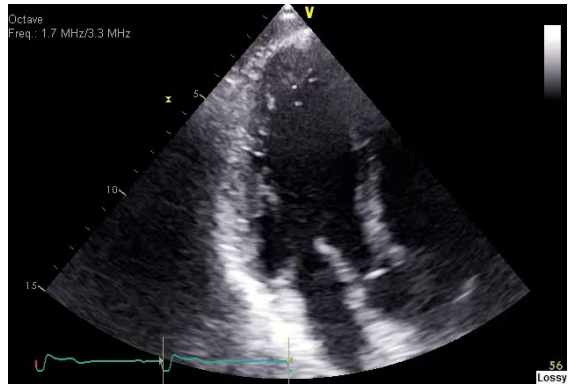
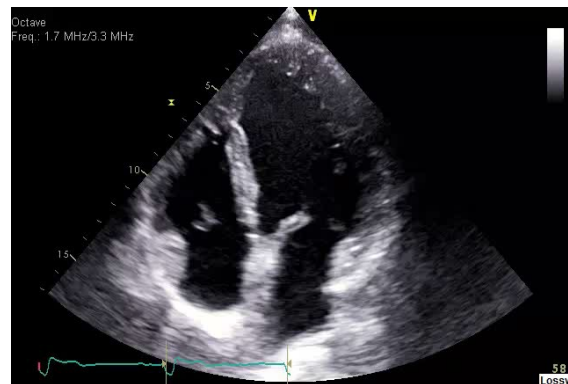
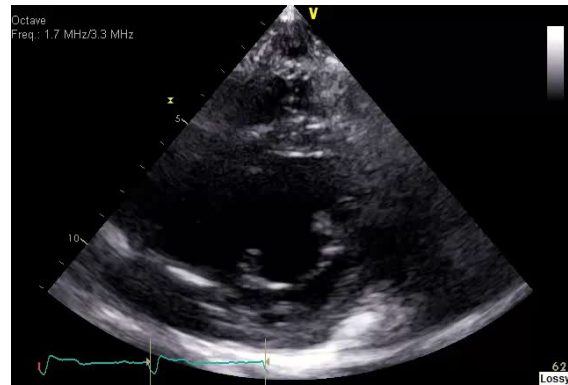
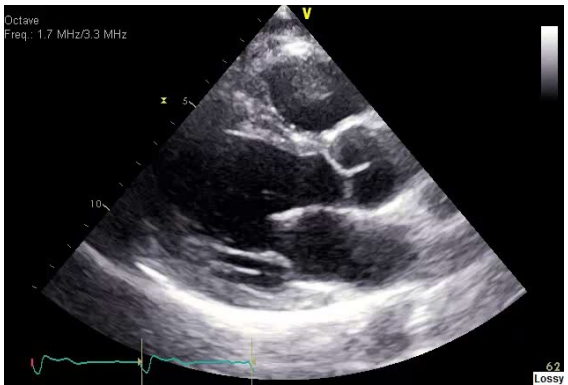
הקריה הרפואית לבריאות האדם



הולטר 12 חיבורים

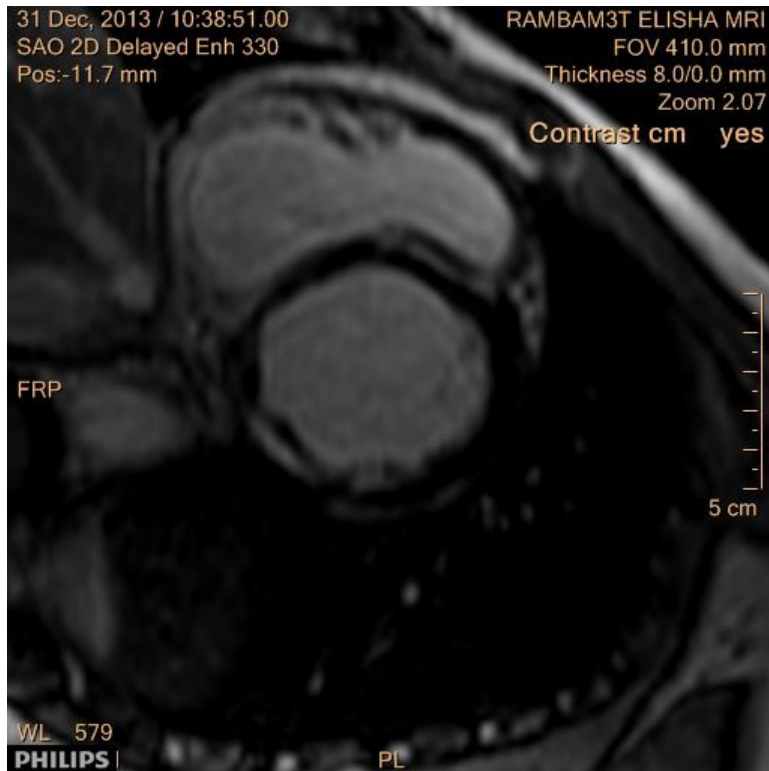


הצגת מקרה אקו לב





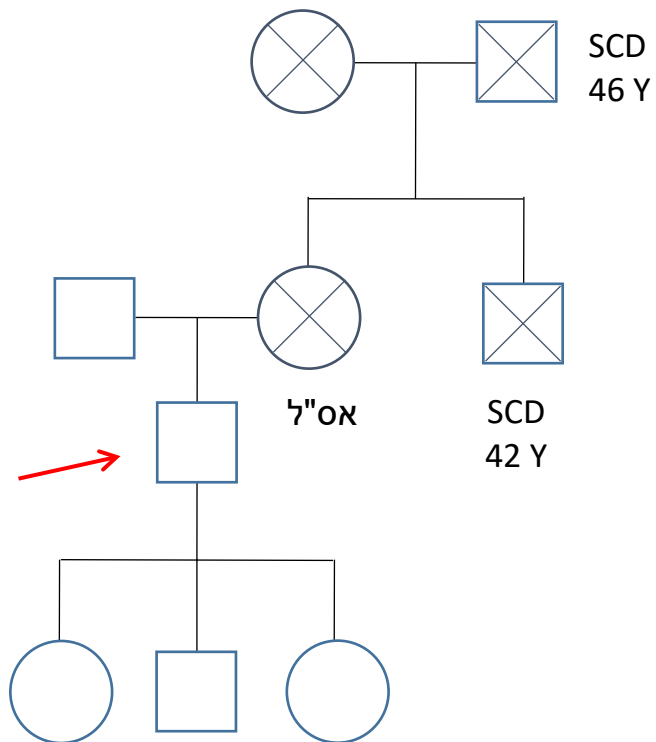
הצגת מקרה MRI לב



- ⊙ Borderline LV size and systolic function
- ⊙ Normal LV wall thickness
- ⊙ Normal RV size and systolic function
- ⊙ Mid-wall delayed enhancement in inferior wall



הצגת מקרה - עץ משפחה





אבחון גנטי בגן LMNA

CAAGGAGGCGAAGCTTCGAGACCT רצף תקין

CAAGGAGGCG~~GAAGCTTC~~GAGACCT

↓ ↓ ↓
C AA

del KLRDL

Ins AK



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

60 %

Left ventricular ejection fraction measurement derived from echocardiogram

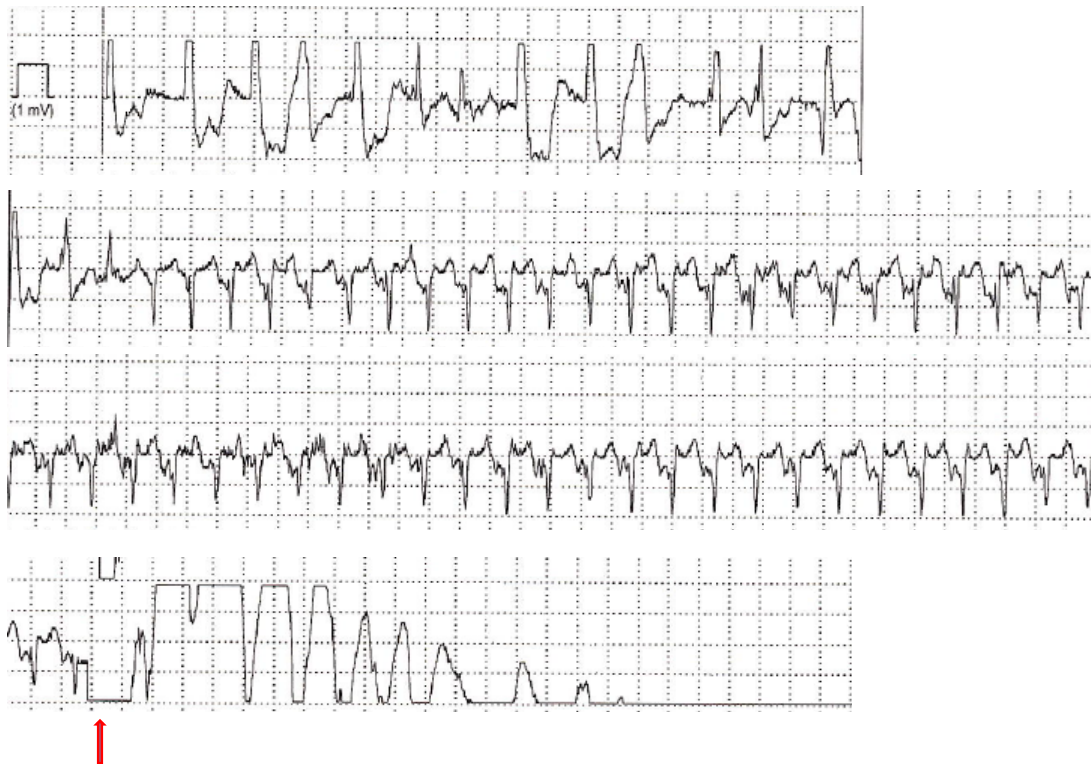
Risk of Life-Threatening Ventricular Tachyarrhythmias at 5 years

42.1 %

[Reset](#)



Eight years later EF=50-55%





The challenge to preserve EF and to prevent CHF

Table 1

Echocardiographic results at 16 weeks of age for *Lmna*^{H222P/H222P} mice treated with placebo (DMSO), benazepril or selumetinib ($n = 7$ mice per group); values are means $\pm$ standard errors of means.

Drug	HR (/min)	LVEDD (mm)	LVESD (mm)	FS (%)
DMSO	498 $\pm$ 7	4.0 $\pm$ 0.2	3.3 $\pm$ 0.4	19.0 $\pm$ 5.9
Benazepril	497 $\pm$ 9	3.9 $\pm$ 0.2	2.9 $\pm$ 0.1	25.8 $\pm$ 2.4*
Selumetinib	501 $\pm$ 9	3.7 $\pm$ 0.2	2.8 $\pm$ 0.1*	30.7 $\pm$ 5.3**

HR, heart rate; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; FS, left ventricular fractional shortening. * $P < 0.05$, ** $P < 0.005$ compared to DMSO.



Mitogen-Activated Protein Kinase Inhibitors Improve Heart Function in Cardiomyopathy Caused by Mutation in Lamin A/C Gene

Table. Echocardiographic Data at 20 Weeks of Age for *Lmna*^{+/+} Mice and *Lmna*^{H222P/H222P} Mice Treated With DMSO Placebo or Treated With SP600125 or PD98059

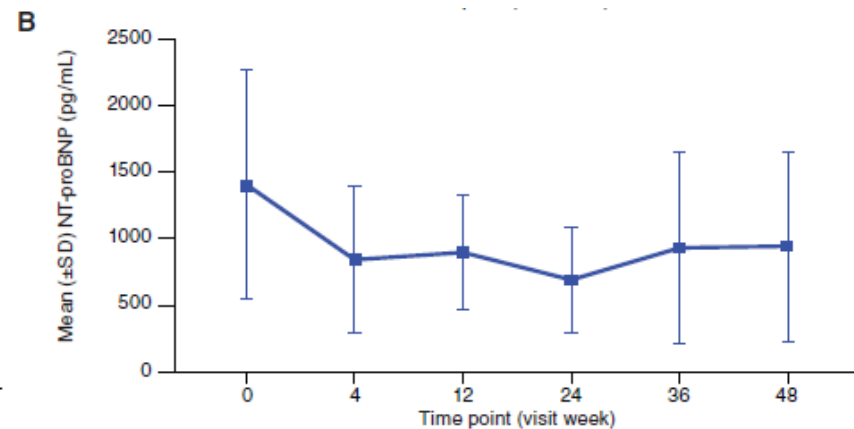
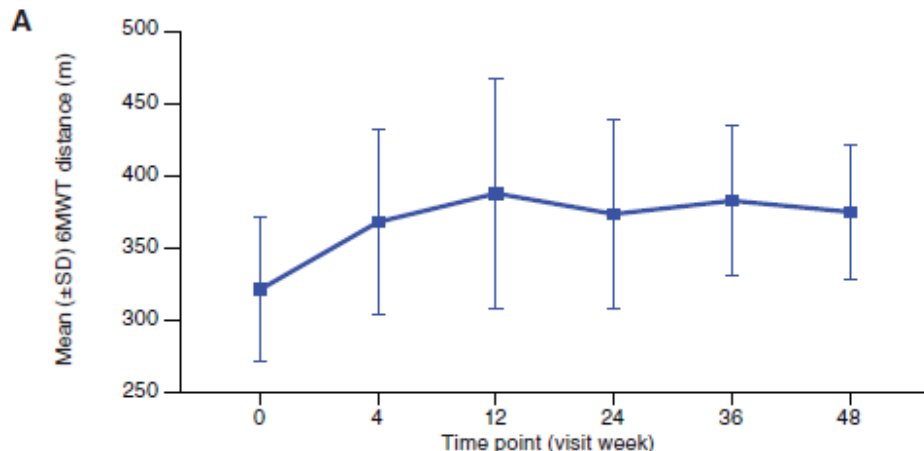
Genotype (Treatment Group)	n	HR, bpm	LVEDD, mm	LVESD, mm	EF, %	FS, %
<i>Lmna</i> ^{+/+}	12	400	3.50±0.06	2.07±0.08	73.21±1.17	41.71±1.01
<i>Lmna</i> ^{H222P/H222P} (DMSO)	22	372	3.87±0.11*	3.00±0.13†	53.87±2.58†	27.86±1.54†
<i>Lmna</i> ^{H222P/H222P} (PD98059)	19	350	3.55±0.11	2.41±0.11	65.46±2.64§	35.91±1.88§
<i>Lmna</i> ^{H222P/H222P} (SP600125)	26	363	3.73±0.08	2.67±0.10‡	61.88±1.66§	33.11±1.16§

HR indicates heart rate; FS, fractional shortening. Values are mean±SEM.

Comparison between DMSO-treated *Lmna*^{H222P/H222P} and *Lmna*^{+/+} mice: **P*<0.05, †*P*<0.0005. Comparison between SP600125-treated, PD98059-treated, and DMSO-treated *Lmna*^{H222P/H222P} mice: ‡*P*<0.05, §*P*<0.005, ||*P*<0.0005.



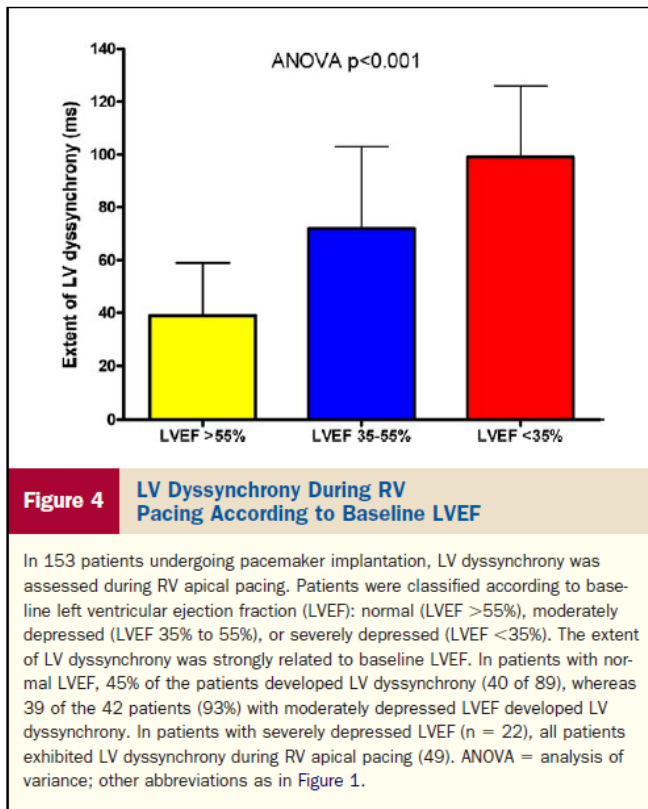
Efficacy and Safety of ARRY-371797 in *LMNA*-Related Dilated Cardiomyopathy: A Phase 2 Study





The challenge to preserve EF

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Tops LF et al JACC 2009; 54: 764-766



The role of early CRT-D implantation in DCM patients with narrow QRS carrying lamin A/C

Indication for a device implantation, n=10

Pacemaker:

Bradycardia, n=4

AV block, n=2

ICD:

Sustained VT, n=3

Primary prevention for high risk, n=1

CRT-D group, n=5

Pacemaker, n=3

ICD, n=2

non CRT-D group, n=5

Pacemaker, n=4

ICD, n=1



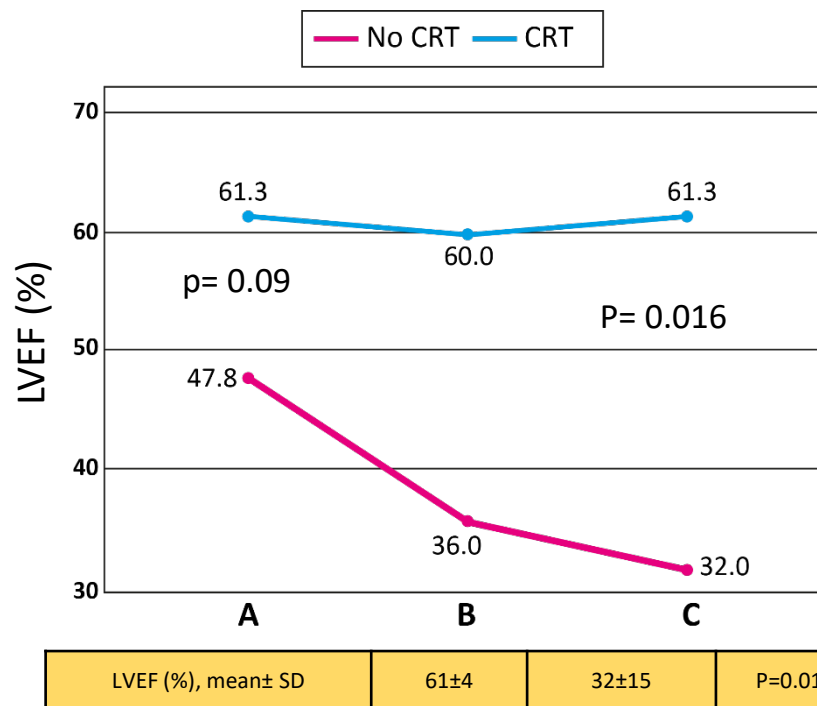
Results

Baseline characteristics of the study population n=10 , at presentation

Variable	CRT-D, n=5	Non CRT-D, n=5	p
Age (mean $\pm$ SD) ,years	53.2 $\pm$ 12	50 $\pm$ 5	N/S
Male, n (%)	4 (80%)	4 (80%)	N/S
Rate, ECG, (mean $\pm$ SD), bpm	42 $\pm$ 12	45 $\pm$ 15	N/S
Max PR, 12l holter, (mean $\pm$ SD) msec	268 $\pm$ 50	280 $\pm$ 0	N/S
QRS duration, mean $\pm$ SD, ms	92 $\pm$ 16	100 $\pm$ 12	N/S
NSVT, 12l holter, n (%)	2 (40%)	2 (40%)	N/S
EF , echocardiography, (mean $\pm$ SD) %	61 $\pm$ 2	47.8 $\pm$ 12	0.09
LVEDD, echocardiography, (mean $\pm$ SD), cm	5.3 $\pm$ 0.3	5.5 $\pm$ 0.2	N/S

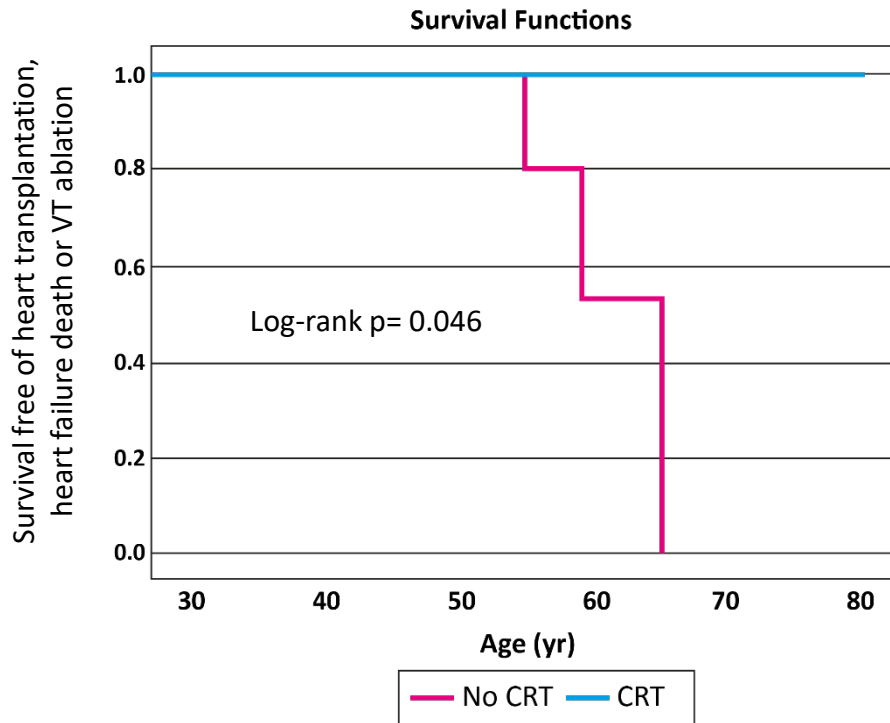


LVEF during the follow up in the CRT and no CRT group follow up 6.4 ± 4 years



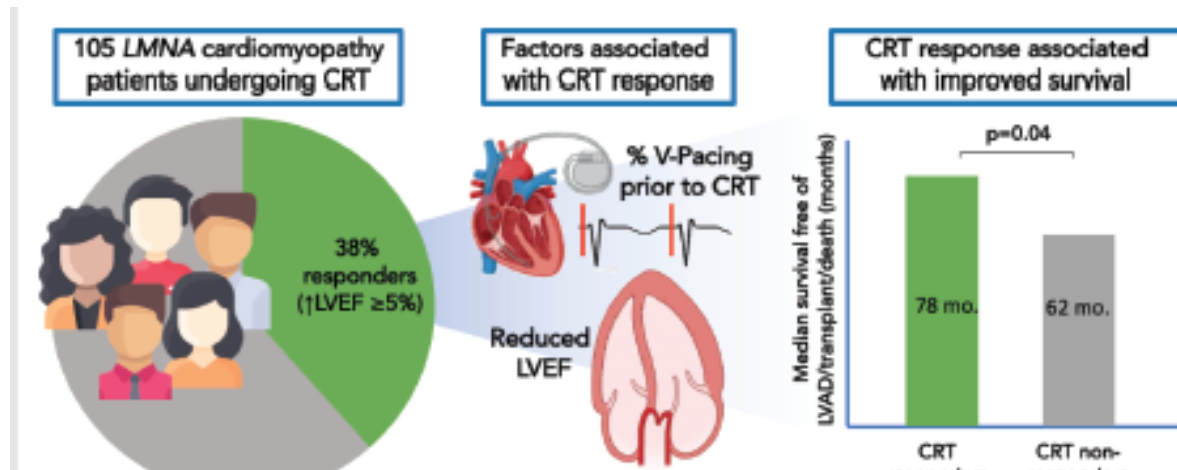


Survival free of heart transplantation, heart failure death or VT ablation

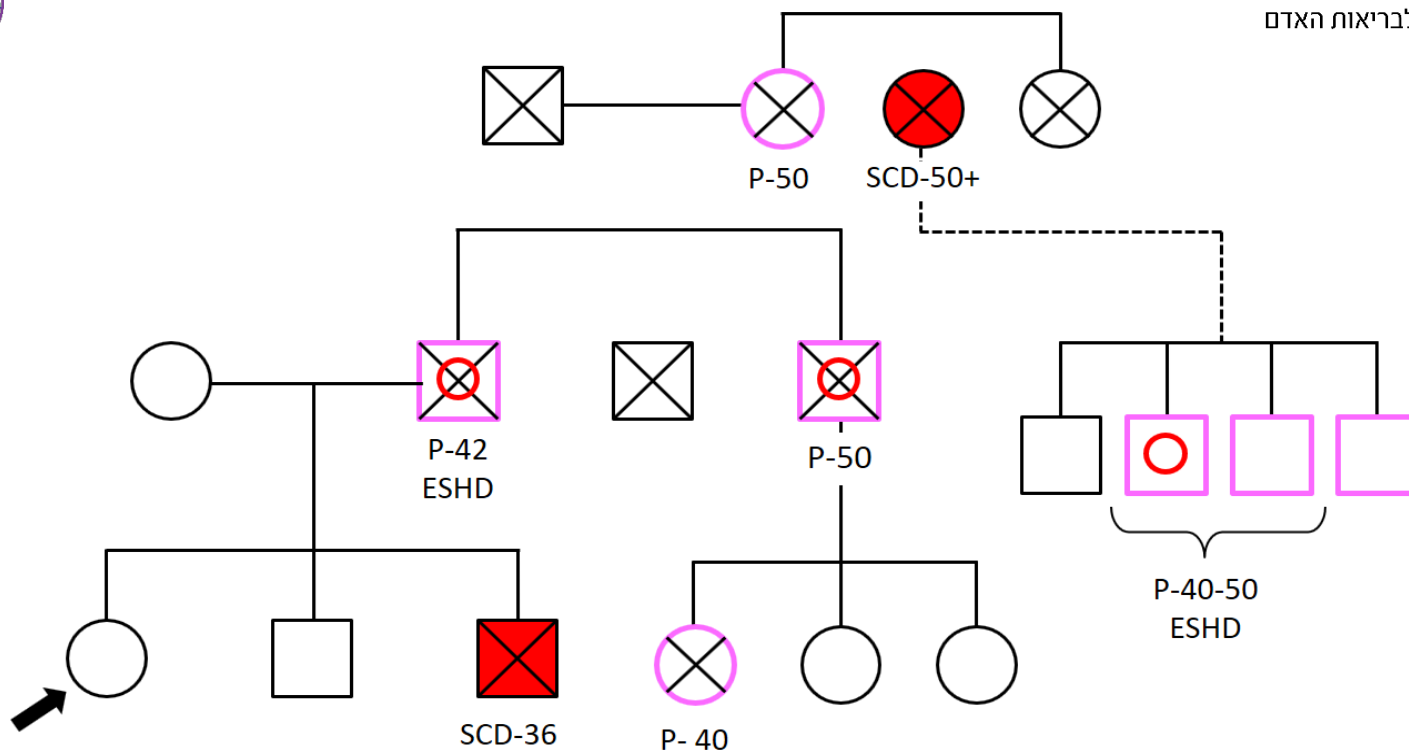




The response to CRT therapy in LMNA cardiomyopathy



Factors associated with improved systolic function and survival amongst LMNA cardiomyopathy patients undergoing cardiac resynchronization therapy (CRT), LVAD, left ventricular assist device: LVEF, left ventricular ejection fraction.



Sudden cardiac death



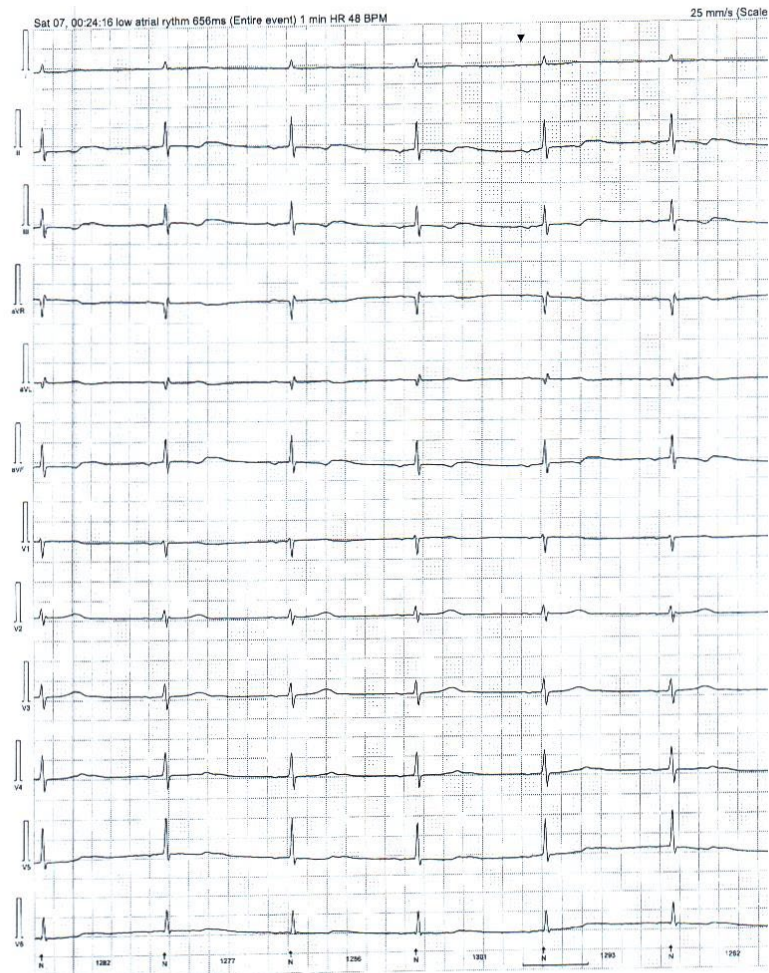
End stage heart disease



Pacemaker

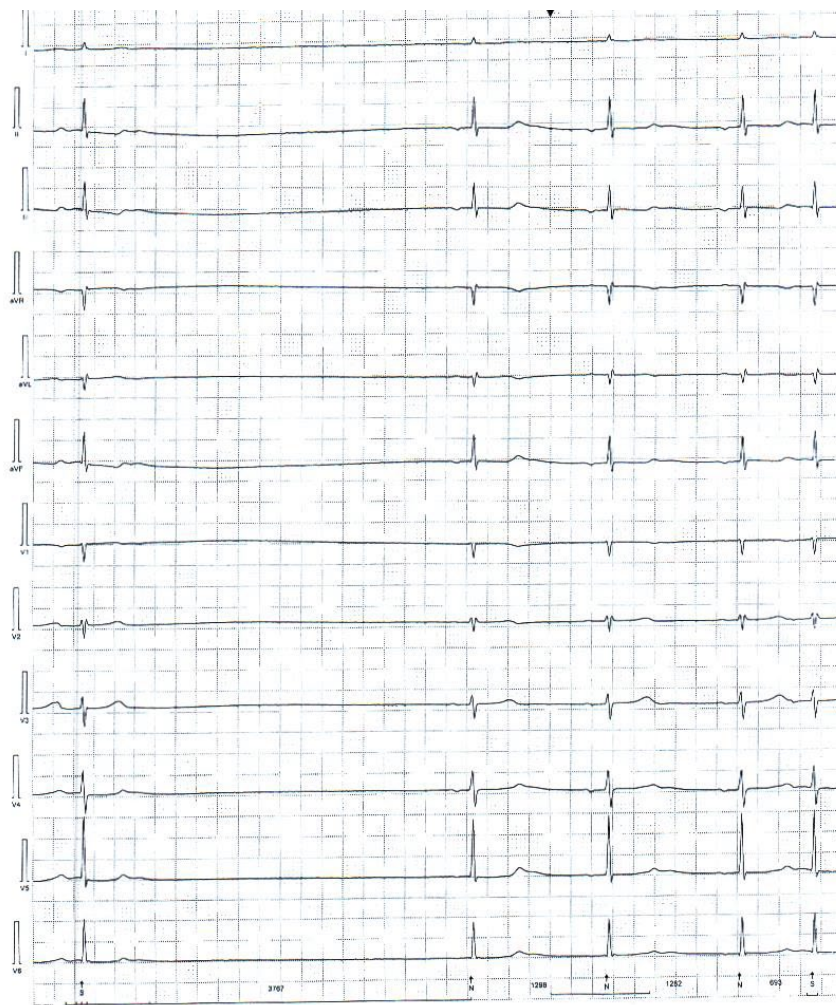






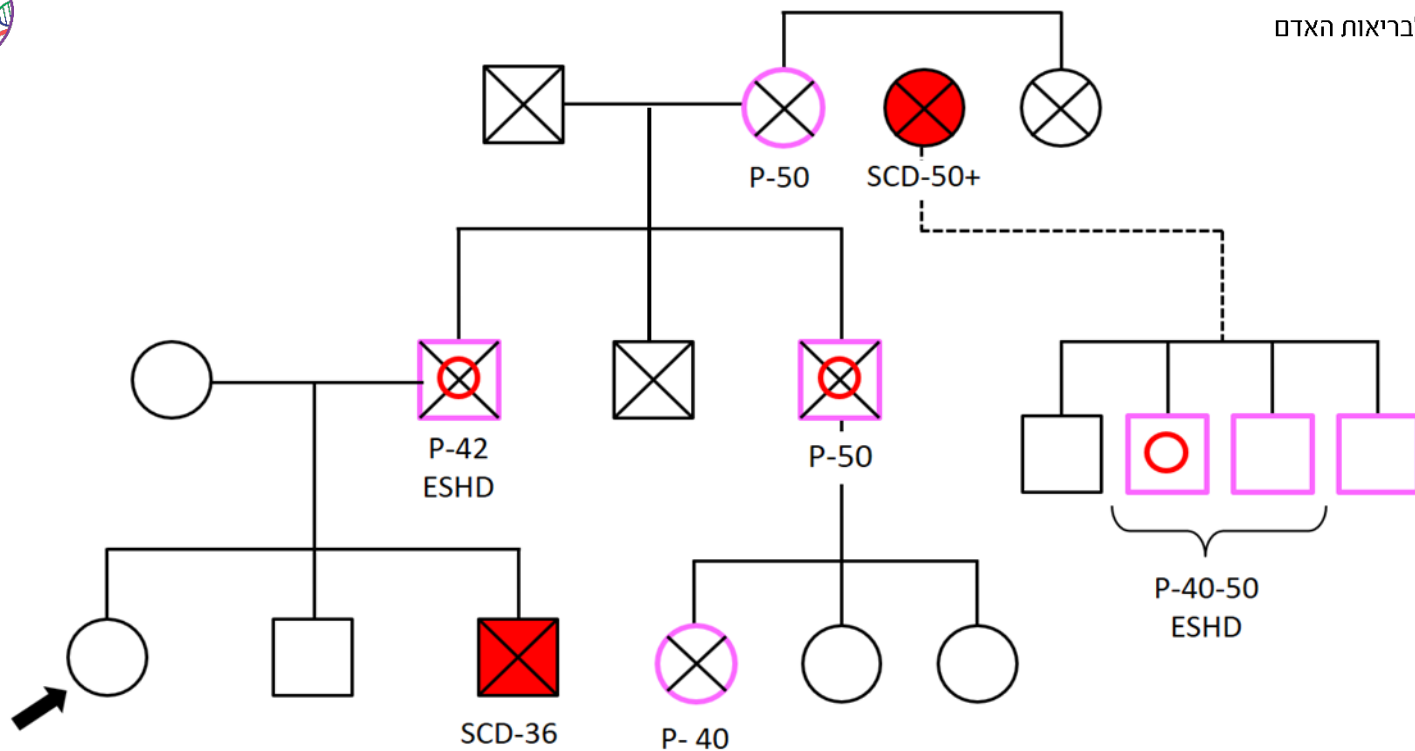
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רמב"ם
הקרית הרפואית לבריאות האדם





Sudden cardiac death  

End stage heart disease  

Pacemaker  



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

14.1 %

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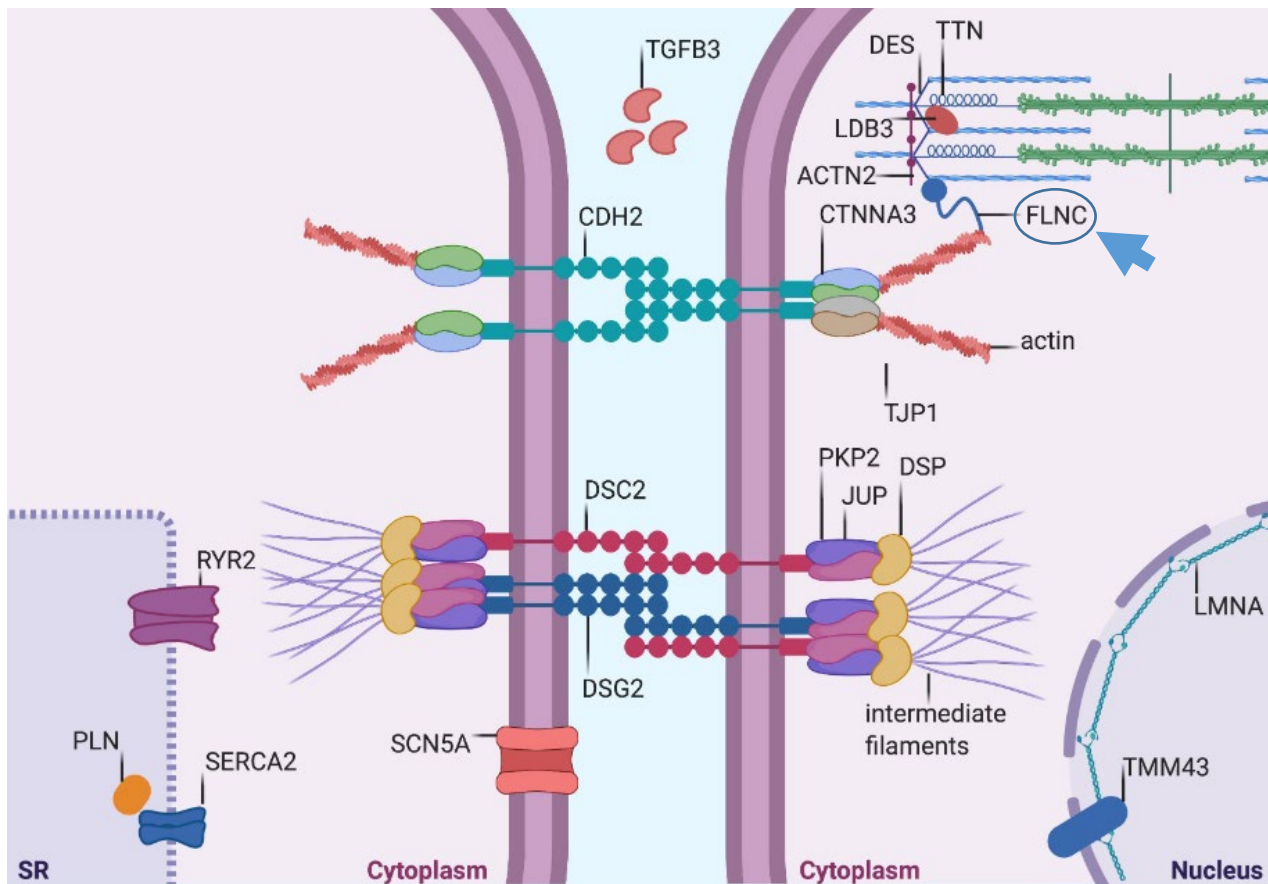
Wahbi et al. Development and Validation of a New Risk Prediction Score for Life-Threatening Ventricular Tachyarrhythmias in Laminopathies. Circulation. 2019 Jul 23;140(4):293-302.



Personalized Medicine in Genetic DCM (Genes related to DCM) (146)

ACTC1, BAG3, DES, DMD, DSP, FLNC, HCN4, LMNA, MYBPC3, MYH7, PKP2, PLN, RBM20, TAZ, TNNC1, TNNI3, TNNT2, TPM1, TTN, ABCC9, ACTA1, ACTN2, ALMS1, ALPK3, ANKRD1, ANO5, ASNA1, CAV3, CHRM2, COL741, CRYAB, CSRP3, DNAJC19, DOLK, DSC2, DSG2, DYSF, EMD, EYA4, FHL2, FHOD3, FKRP, FKTN, FOXD4, GAA, GATA4, GATA6, GATAD1, GLB1, GYG1, HFE, JPH2, JUP, KLF5, LAMA2, LAMA4, LAMP2, LDB3, MURC, MYBPHL, MYH6, MYL2, MYL3, MYOT, MYPN, MYZAP, NEBL, NEXN, NKX2-5, PCCA, PCCB, PLEKHM2, PPA2, PPCS, PRDM16, PSEN1, PSEN2, QRSL1, RAF1, RPL3L, RYR2, SCN5A, SDHA, SGCD, SGCG, SLC22A5, SPEG, TAZ, TBX5, TBX20, TCAP, SYNE1, SYNE2, TBX20, TCAP, TMEM43, TMEM70, TNNI3K, TRIM63, TMPO, TOR1AIP1, TTR, TXNRD2, VCL, XK, ZBTB17, AKT1, BRAF*, CASZ1, CAVIN4, CDC25B, CTF1, DNM1L*, DTNA, FBX032, FHL1, GATA5*, GLA*, GSK3B, HAND1, HAND2, IDH2*, ILK*, ISL1, KAT2B, KLHL24, KCNJ2*, KCNJ8*, JARID2, LEMD2, LMOD2, LRRC10, MEF2C, MIB1, MYLK3, NDUFB11, NNT, NONO, NKX2-5*, NRAP, NUBPL, OBSCN*, OPA3*, PDLIM3*, PDLIM5, PKD2, PPP1R13L, PRKAG2, PTPN11*, RAF1, RBM24, SGCA*, SGCB*, SURF1, TLL2, TMOD1, TUFM.

Yield of Genetic Test 50%





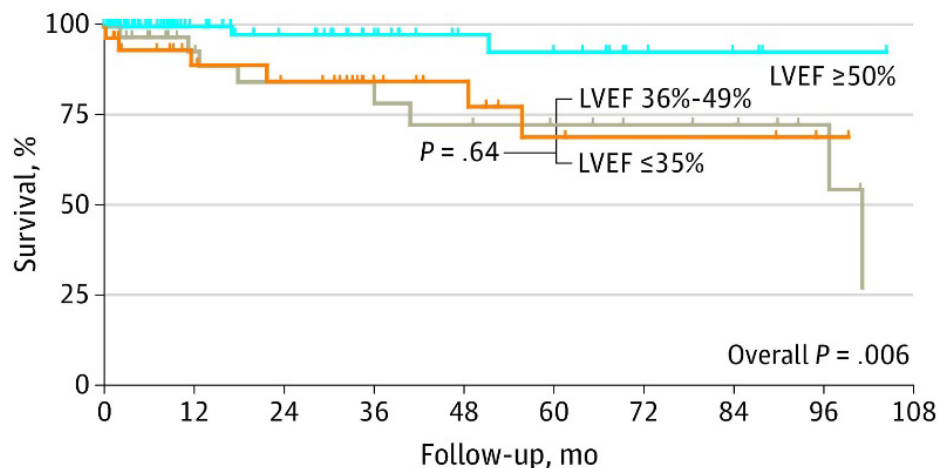
Clinical Characteristics of Carriers of Truncating Mutations in FLNC (n= 82)

		Evaluated	Positive finding	%
Arrhythmia	PVC (>500/24)	55	33	60
	NSVT	55	28	51
	SVT	55	10	18
Events	Sudden death	82	12	15
	Appropriate ICD shock	82	8	10



Survival free from arrhythmic end point in DCM patients carrying FLNC truncated mutation n=167

Survival free from secondary composite arrhythmic end point



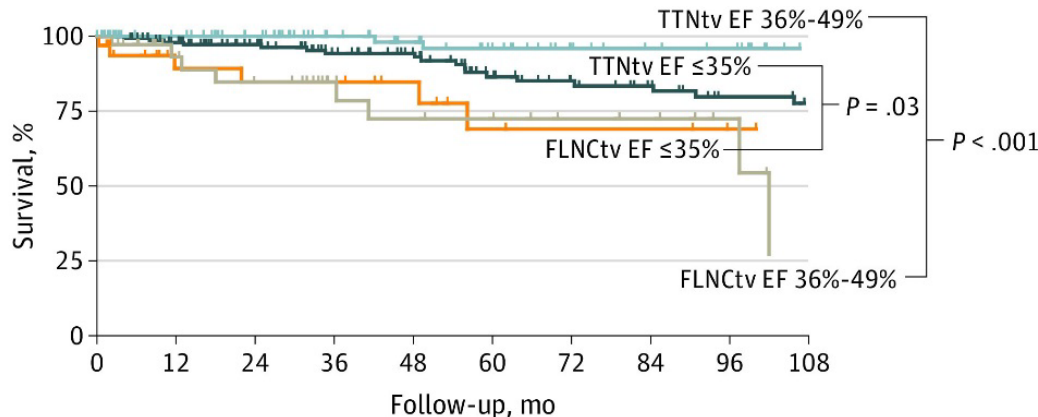
No. at risk

LVEF $\geq 50\%$	95	50	38	28	20	19	13	12	9	8
LVEF 36%-49%	36	22	19	15	12	10	8	7	4	1
LVEF $\leq 35\%$	33	21	19	15	12	7	6	6	4	3



Survival free from arrhythmic end point in DCM patients carrying FLNC truncated mutation and TTN truncated mutation

Survival free from secondary composite arrhythmic end point, by genetic variant



No. at risk

TTNtv EF 36%-49%	86	81	71	55	46	37	28	24	22	13
FLNCtv EF 36%-49%	36	22	19	15	12	10	8	7	4	1
TTNtv EF ≤35%	158	129	108	89	79	60	53	46	39	36
FLNCtv EF ≤35%	33	21	19	15	12	7	6	6	4	3



לסיכום

- **חולי DCM , אתגר בטיפול**
- **האבחון הגנטי הינו פתח לרפואה מותאמת אישית**
- **מאפשר טיפול מיטבי במניעת דום לב ואי ספיקת לב**
- **חשיבות המחקר הקליני והבסיסי**



רמב"ם
הקריה הרפואית לבריאות האדם



**Rambam Health Care Campus,
Haifa, Israel**

Thank you

המרפאה להפרעות קצב תורשתיות



מרפאה קלינית
המעבדה לביצוע בדיקות גנטיות בשיתוף המכון הגנטי
מחקר בתחום

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