The Role of Genetic Testing in the Diagnosis and Management of Cardiomyopathies

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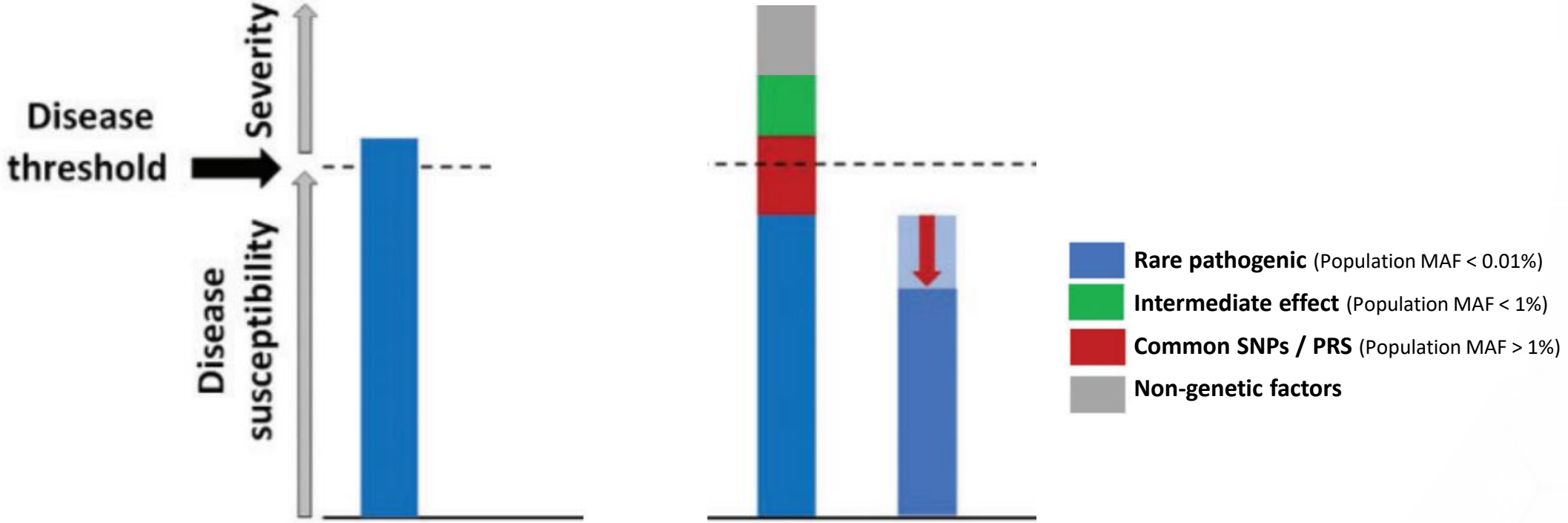
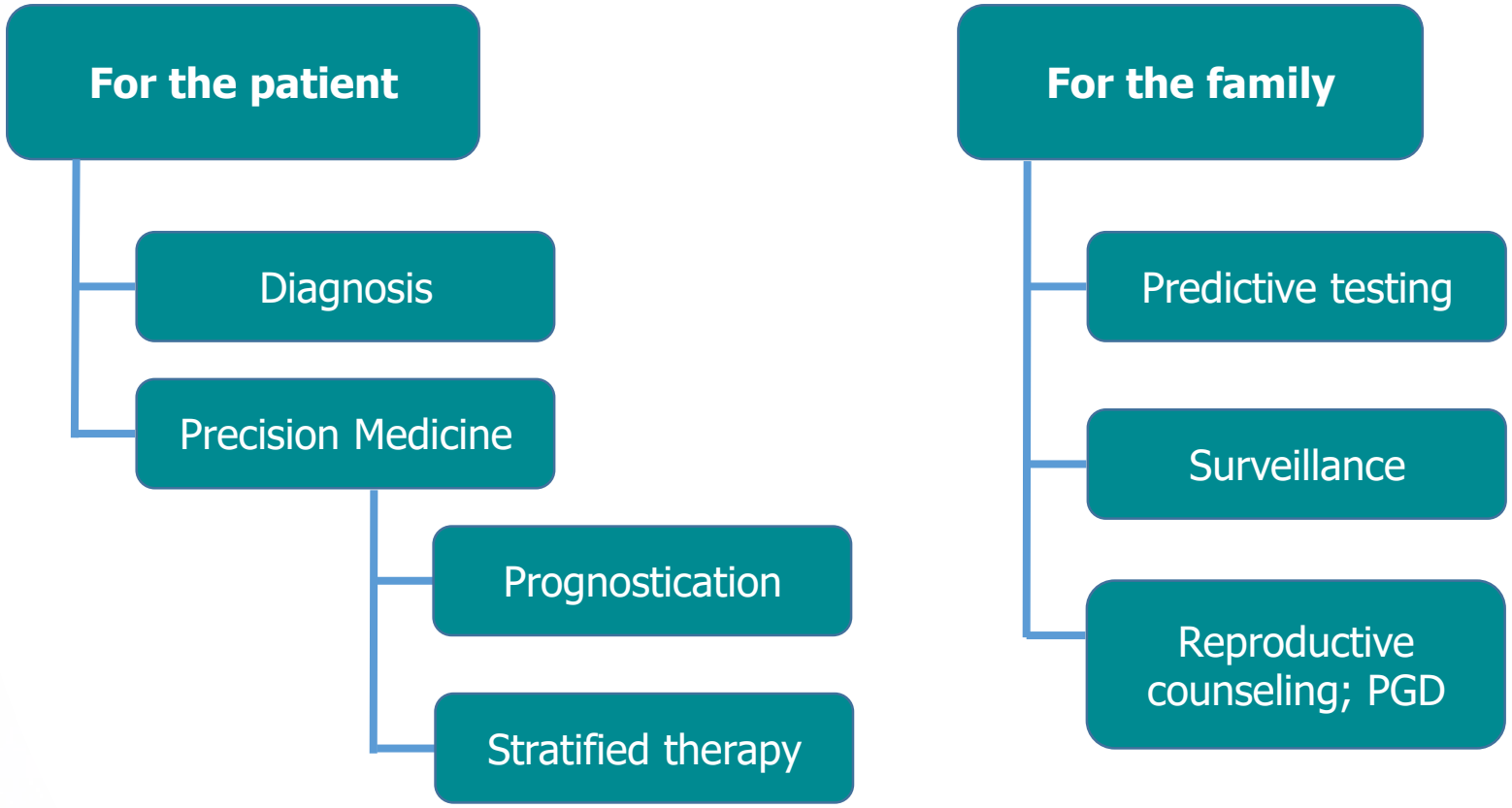
Principles of genomics in inherited cardiovascular conditions

Rare Mendelian Variant

1. 50% chance of inheritance in autosomal dominant disease
2. Mutation present at birth but disease often manifest later on
3. Incomplete penetrance
4. Variable expressivity

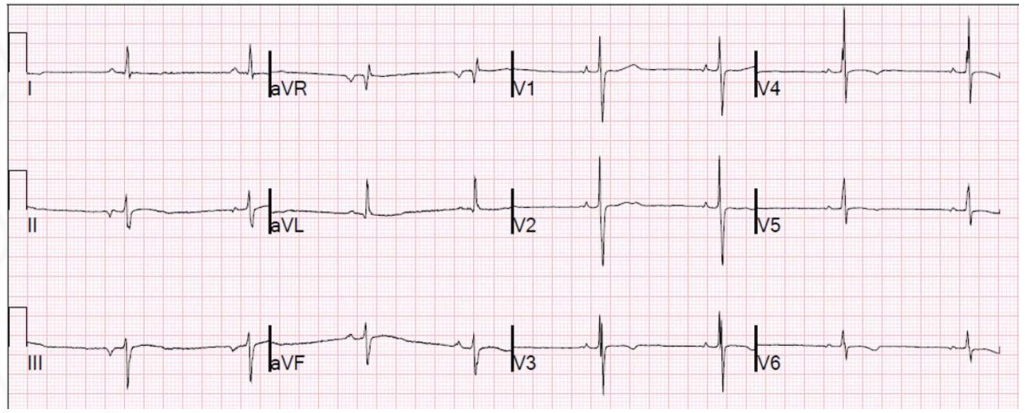


Clinical applications of genomics in inherited cardiovascular conditions

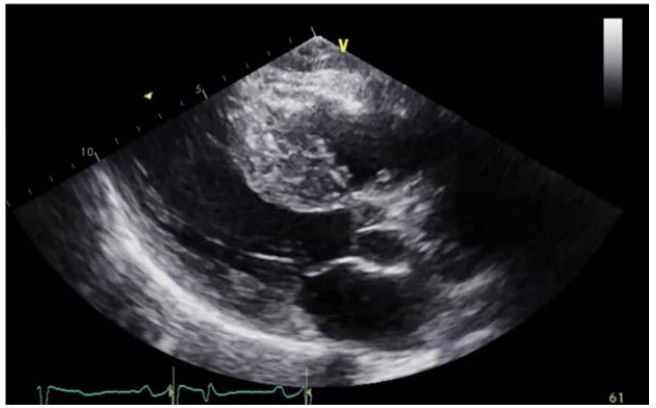


Case 1: ♂ 35 y.o, non-competitive athlete, asymptomatic → screening

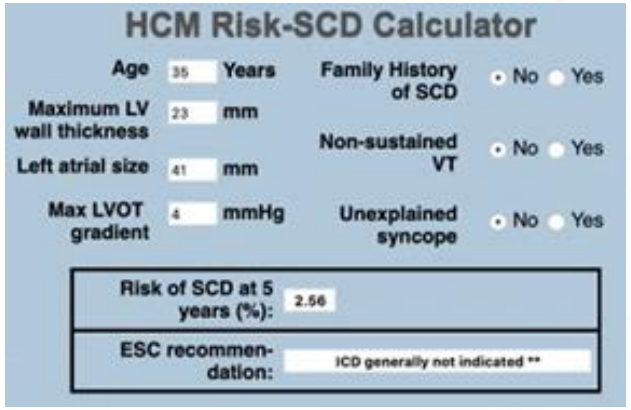
ECG: Lateral TWI



Echo: ASH 23mm



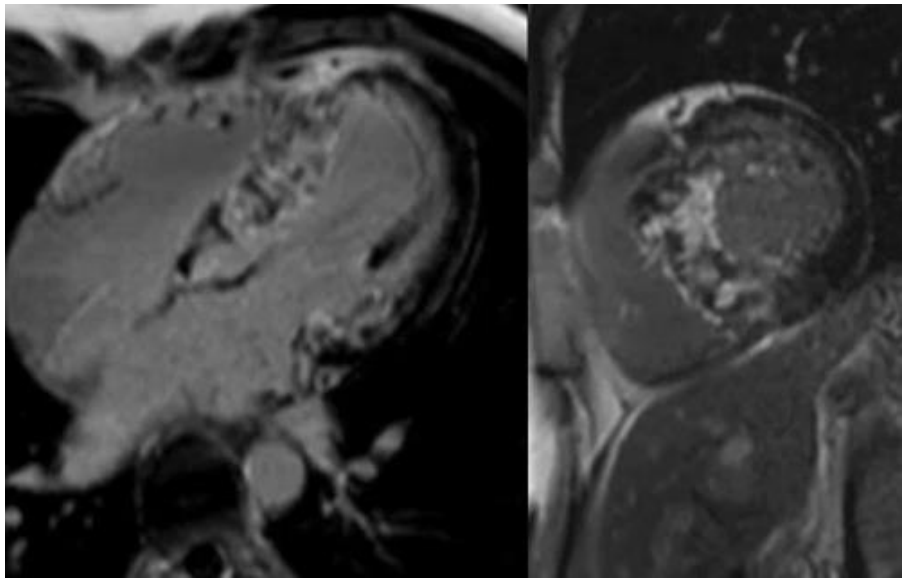
5-year-risk: 2.56%



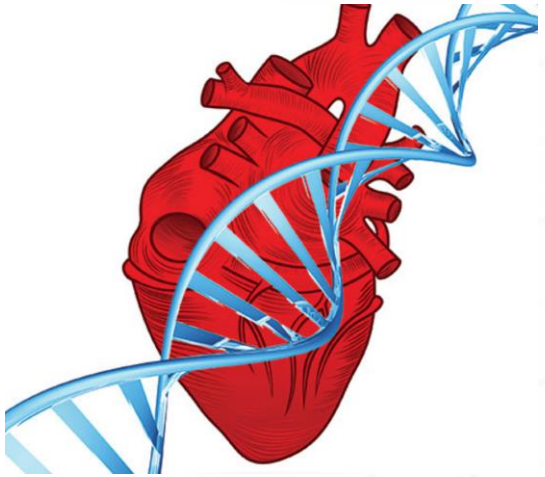
Tools for -

1. **Diagnosis clarification**
2. **Risk refinement**

CMR: Extensive fibrosis



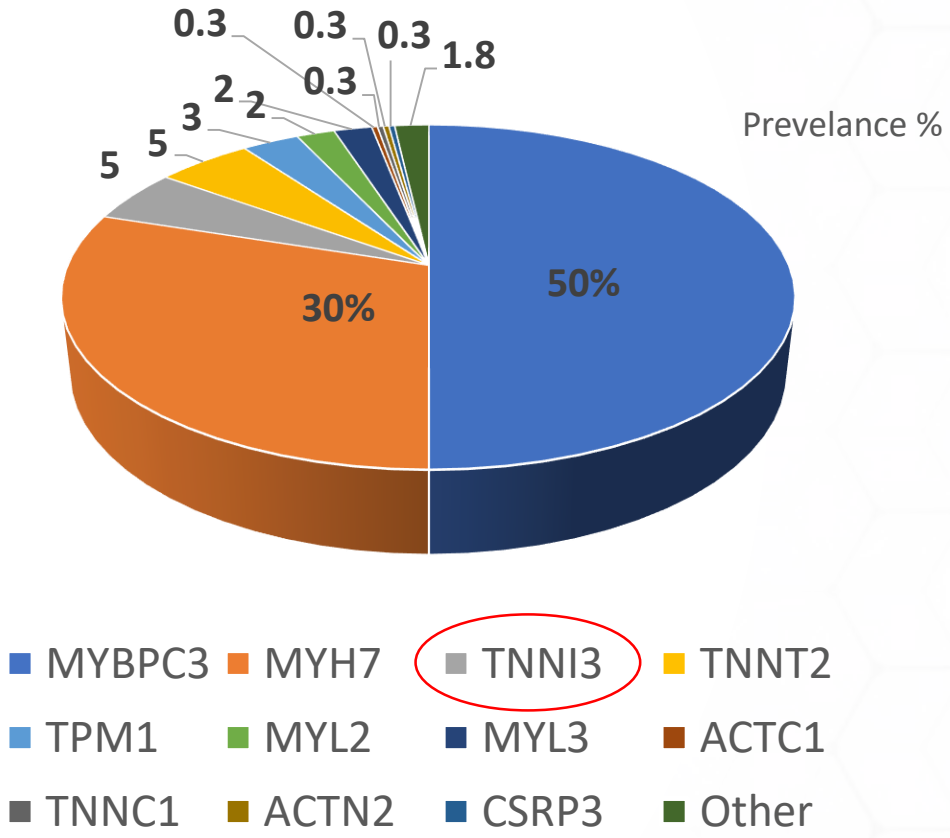
Pathogenic mutation in TNNI3



Hypertrophic Cardiomyopathy: Prognosis

"There are no strong associations between genotype and prognosis"

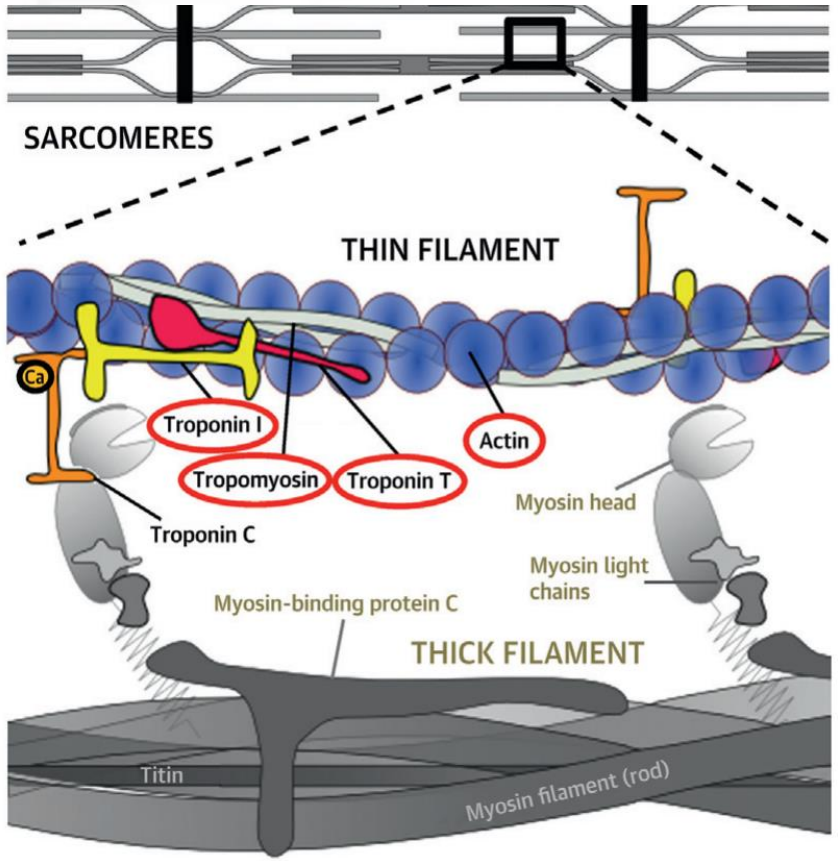
"Genetics is a potential modifier"

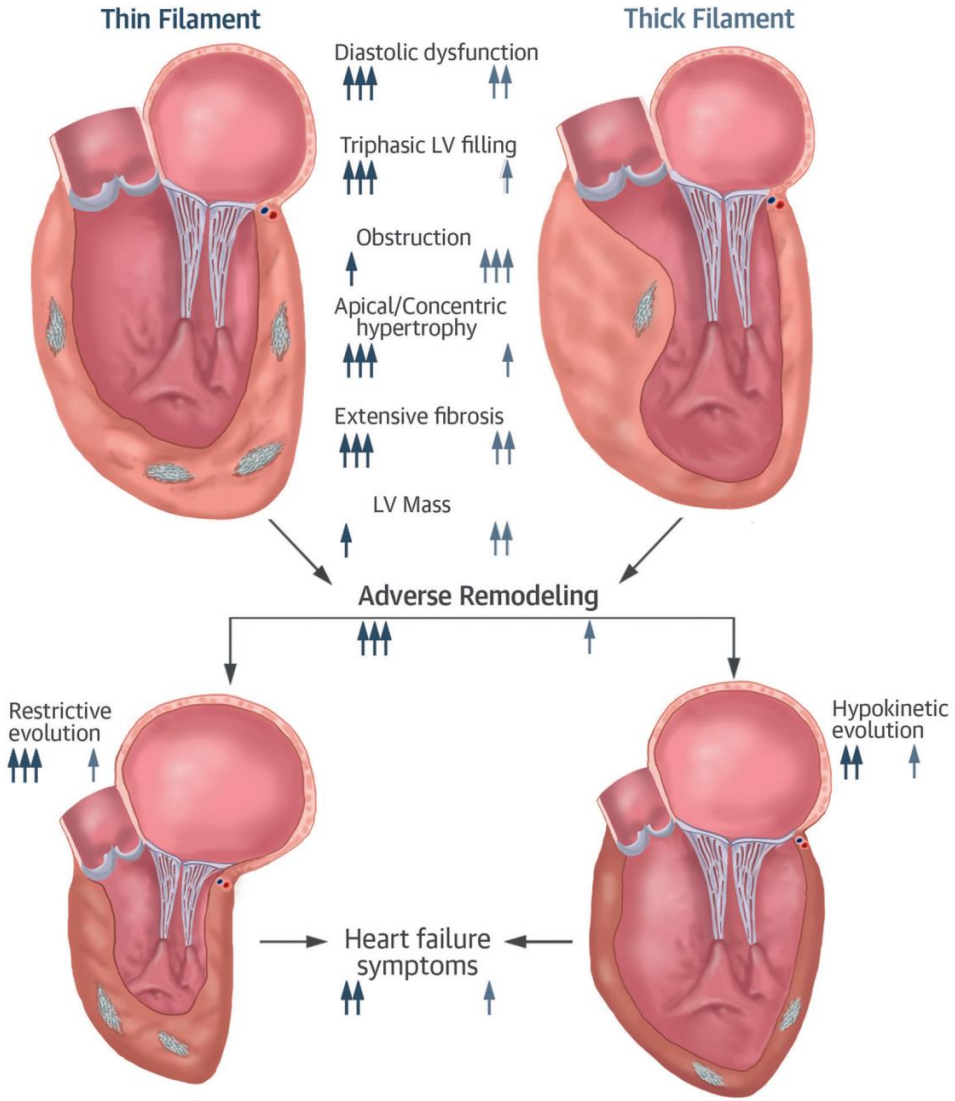


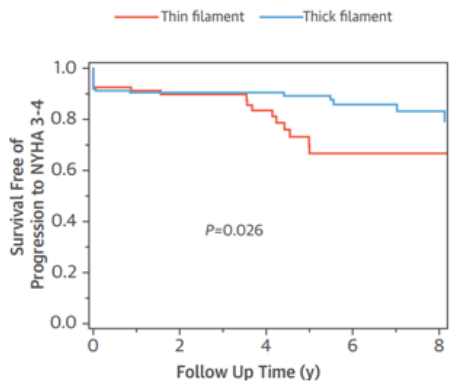
Bos JM Mayo clinic proc 2014 ; M. Ahluwalia, BMJ, 2015; HCM GL on HCM, 2014

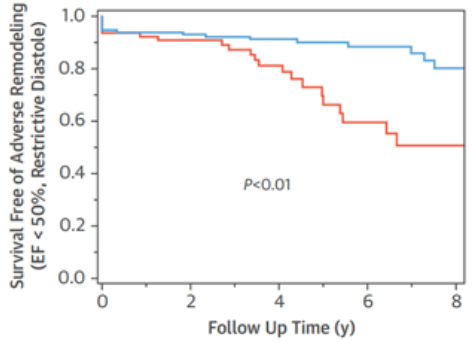
Hypertrophic Cardiomyopathy: Prognosis

Thin-Filament Gene Mutations



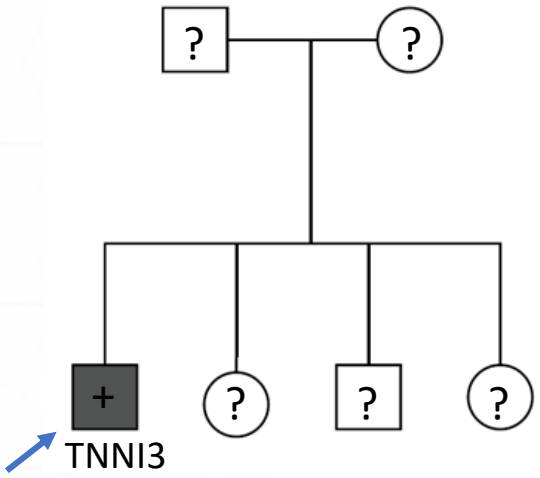


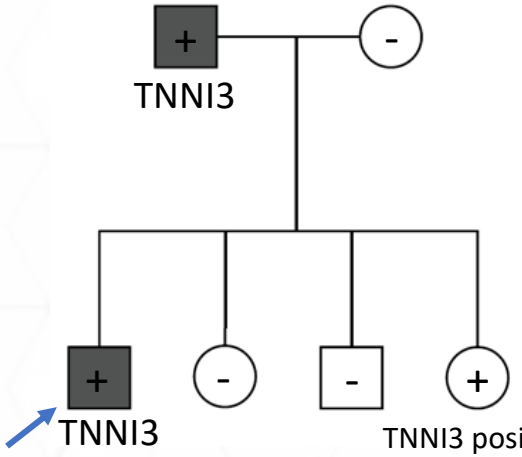




Coppini R et al, JACC 2014

Hypertrophic Cardiomyopathy: Predictive testing



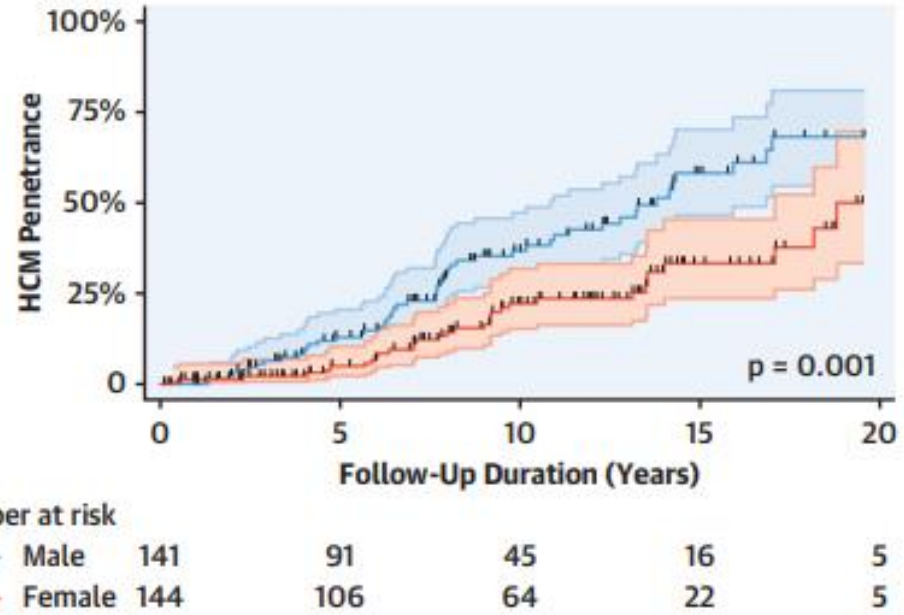


TNNI3 positive
Phenotype negative

CENTRAL ILLUSTRATION **Kaplan-Meier Estimates of Penetrance of Hypertrophic Cardiomyopathy in the Study Cohort by Sex**

285 adult and pediatric carriers of pathogenic/likely pathogenic sarcomere protein variants with no hypertrophic cardiomyopathy (HCM)

Penetrance of HCM at 15-year follow-up: 46% (95% CI: 38%-54%)



Risk factors for HCM

Male
HR: 2.91
(95% CI: 1.82-4.65)

Abnormal ECG
HR: 4.02
(95% CI: 2.51-6.44)

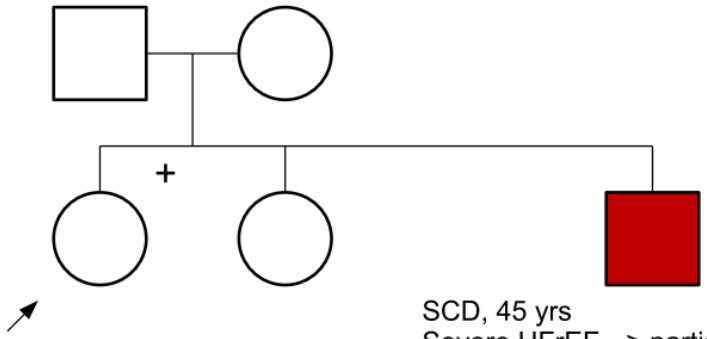
Lowest risk for HCM

TNNI3 variants
HR: 0.19
(95% CI: 0.07-0.55)

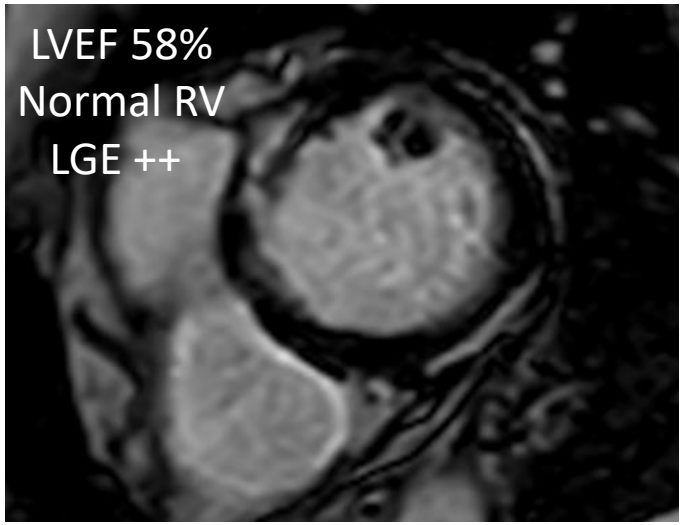
Lorenzini, M. et al. J Am Coll Cardiol. 2020;76(5):550-9.

Male sex and abnormal electrocardiogram are risk factors for penetrance of hypertrophic cardiomyopathy (HCM) in carriers of pathogenic/likely pathogenic variants in sarcomere genes, while *TNNI3* variants are protective.

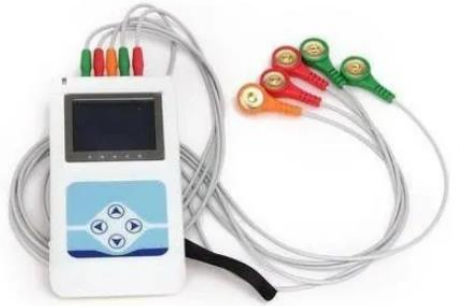
Case 2: ♀ 40 y.o, healthy, asymptomatic, FHx of SCD in brother



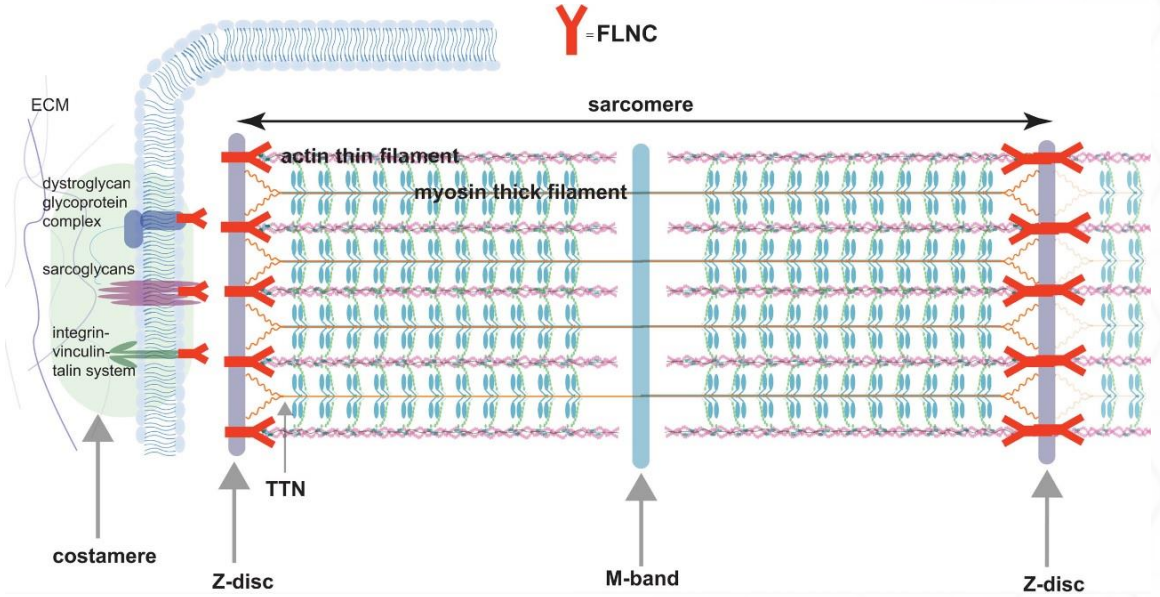
SCD, 45 yrs
Severe HFrEF --> partially recovered to 50%
PVCs presumed from LV summit –> ablated
No MRI/ No Genetics / ICD implanted



NSVT
Few PVCs

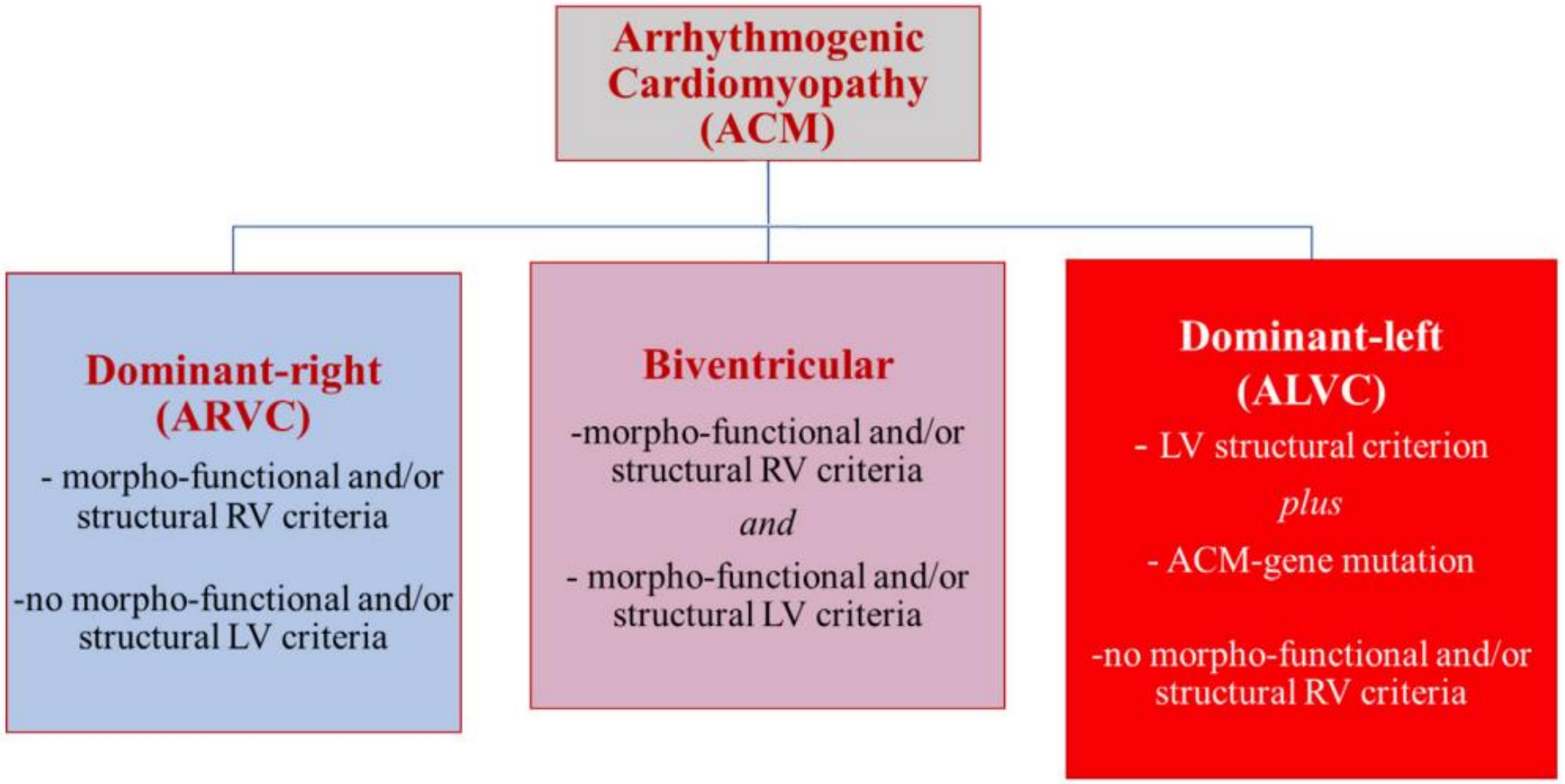


Pathogenic mutation in Filamin C (FLNC)



R. Agarwal et atl, Circ. Res. 2021

Arrhythmogenic Cardiomyopathy (ACM): Diagnosis



D. Corrado et al. 2020, Diagnosis of arrhythmogenic cardiomyopathy: The Padua criteria

ACM/DCM: Prognosis

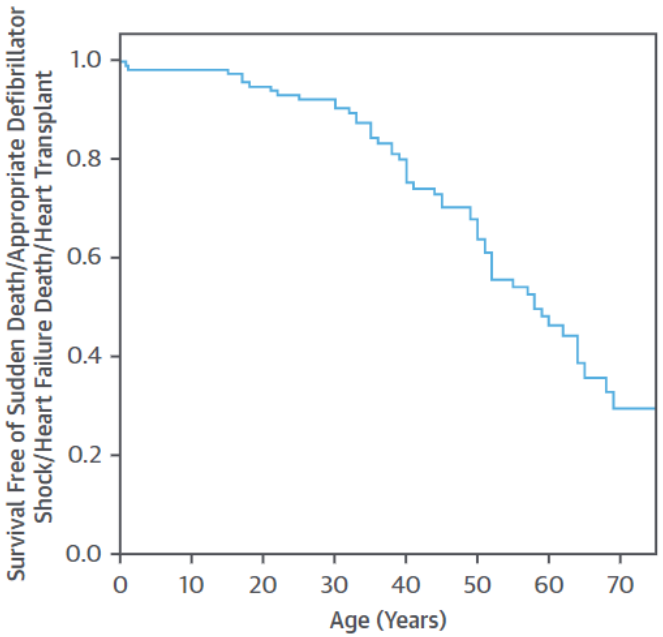
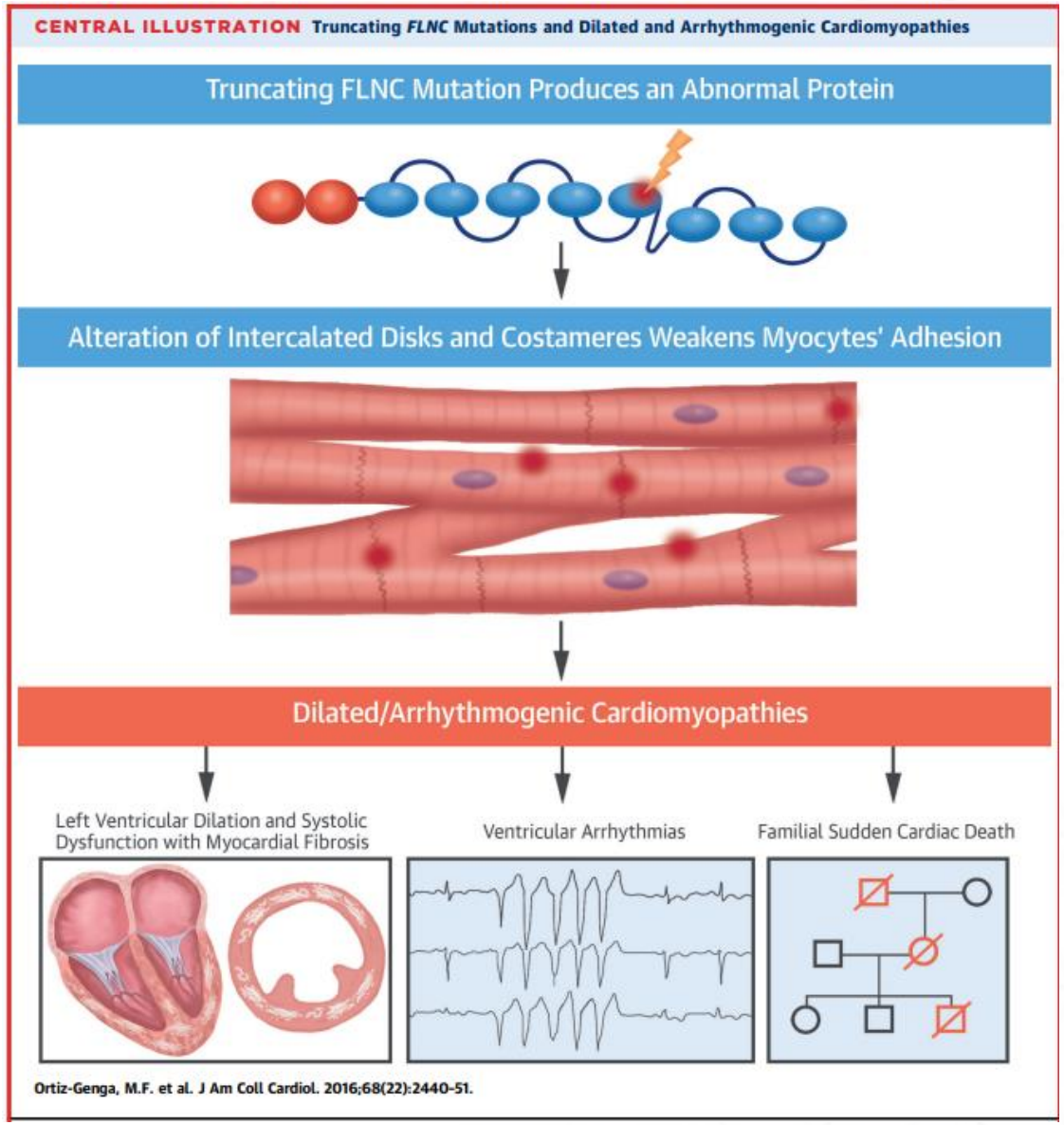


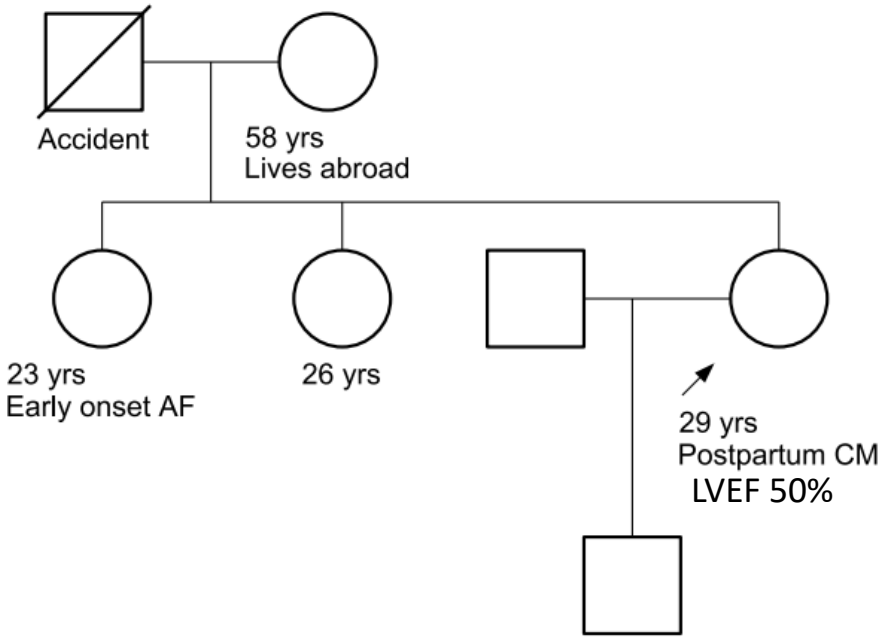
TABLE 1 Clinical Characteristics of Carriers of Truncating Mutations in *FLNC*

	Probands (n = 28; 17 Male)			Relatives With the Mutation (n = 54; 28 Male)			All Carriers (n = 82; 45 Male)		
	Evaluated	Positive Finding	%	Evaluated	Positive Finding	%	Evaluated	Positive Finding	%
Events									
Sudden death	28	5	18	54	7	13	82	12	15
Appropriate ICD shock	28	4	14	54	4	7	82	8	10
Heart failure death	28	0	0	54	0	0	82	0	0
Heart transplantation	28	5	18	54	0	0	82	5	6
Stroke	28	2	7	54	0	0	82	2	2

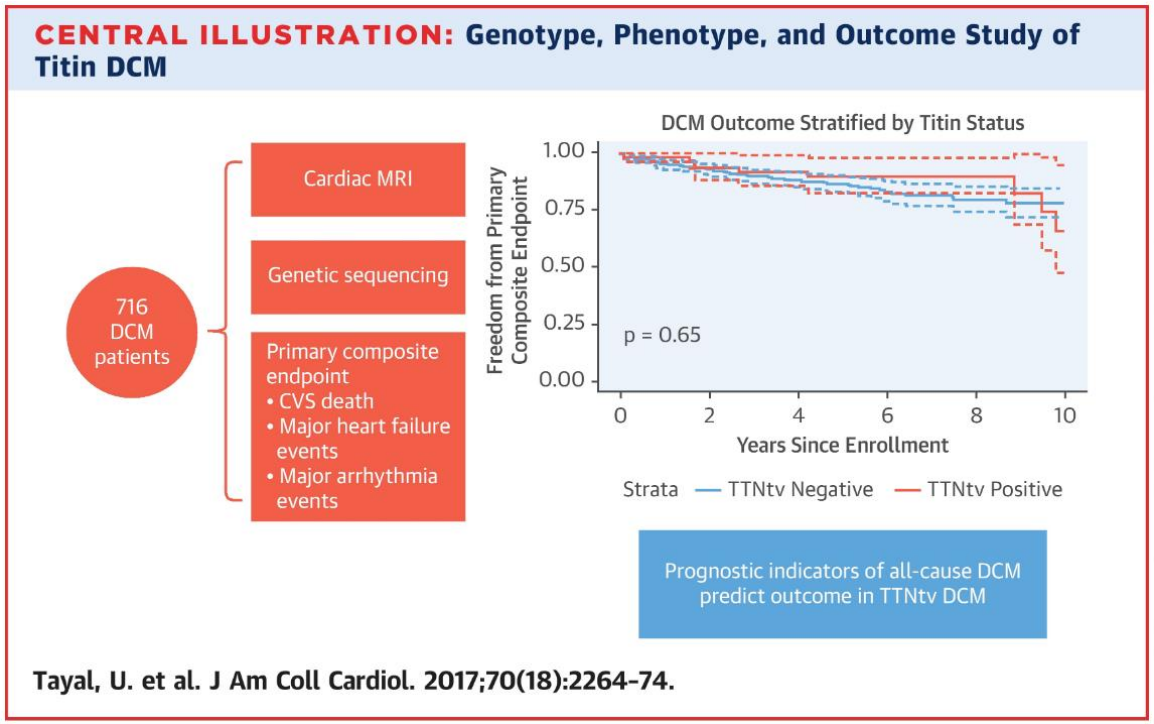


Ortiz-Genga et al, JACC 2016

Case 3: ♀ 29 y.o, post-partum CM, LVEF 50%, LVEDD: upper normal

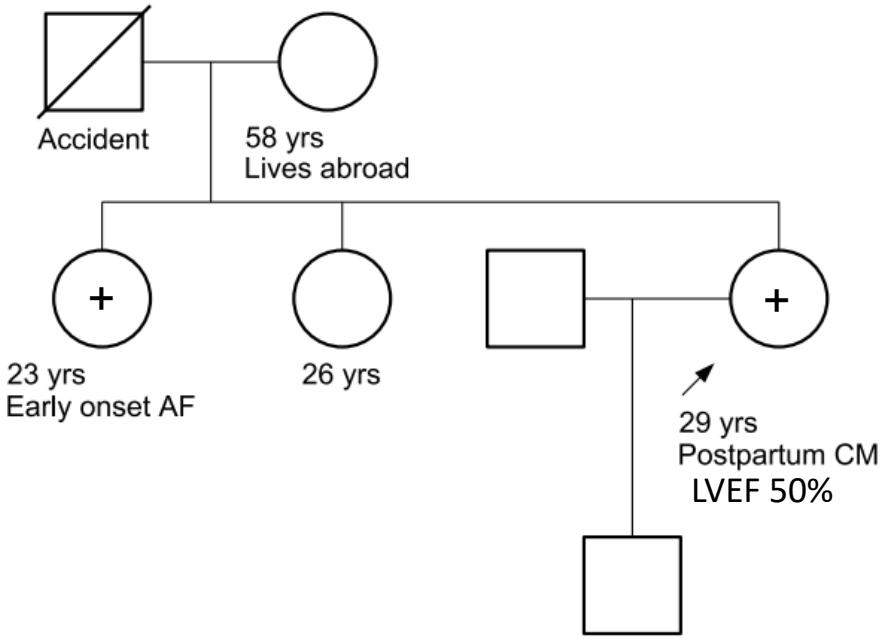


- 15-20% of PPCM carry a pathogenic DCM mutation
- Undiagnosed preexisting CM or develop/worsen peri-partum
- Most commonly implicated gene: Titin (TTN)



Tayal et al, JACC 2017James S Ware, NEJM 2016, K Sliwa, EHJ 2021

Early-onset atrial fibrillation



Pre-implantation
Genetic Diagnosis (PGD)

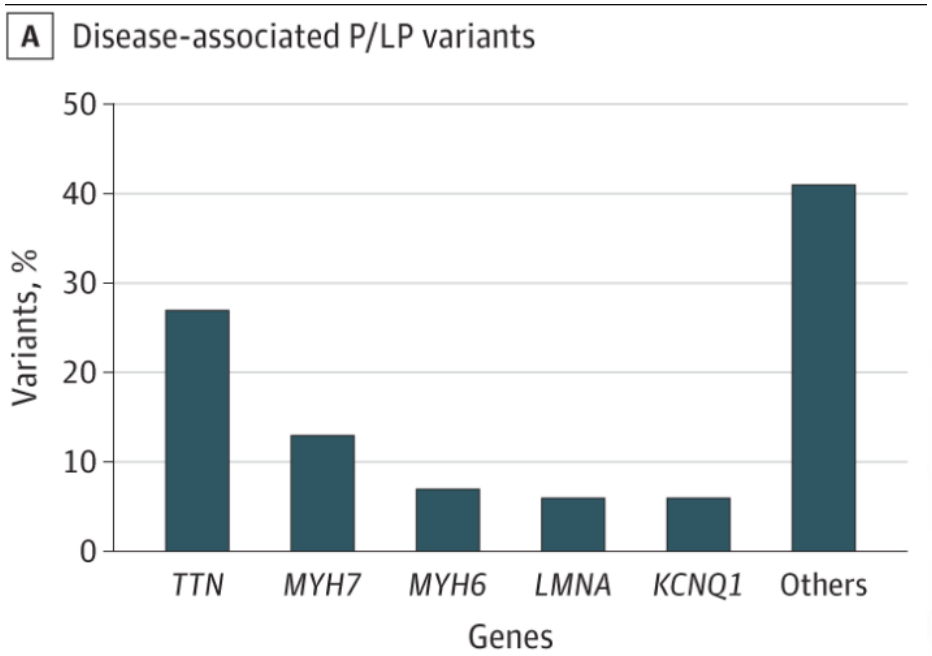
Original Investigation

September 8, 2021

Early-Onset Atrial Fibrillation and the Prevalence of Rare Variants in Cardiomyopathy and Arrhythmia Genes

Zachary T. Yoneda, MD, MSCI[1]; Katherine C. Anderson, MS, CSG[1]; Joseph A. Quintana, MD[1]; et al

Disease-associated rare variants in 17% of patients under 30 y.o



Zachary et al JAMA Cardiology 2021

Summary: Genetic testing in Cardiomyopathies

- Clarify diagnosis
- Differentiate phenocopies (e.g. Fabry, Danon)
- A negative result of genetic testing also has value
- Prognosis and therapy
- Facilitate predictive testing
- Prenatal diagnosis

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