11th ANNUAL HEART FAILURE UPDATE 2024

Friday May 24 - Saturday May 25

Marriott Chateau Champlain, Montreal, Quebec

CHFS SCIC

Canadian Heart Failure Society
Société canadienne d'insuffisance cardiaque

𝕏 @CanHFSociety #HFupdate

CLINICAL CONUNDRUMS IN GENETIC CARDIOMYOPATHY

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HiRO

nova scotia health

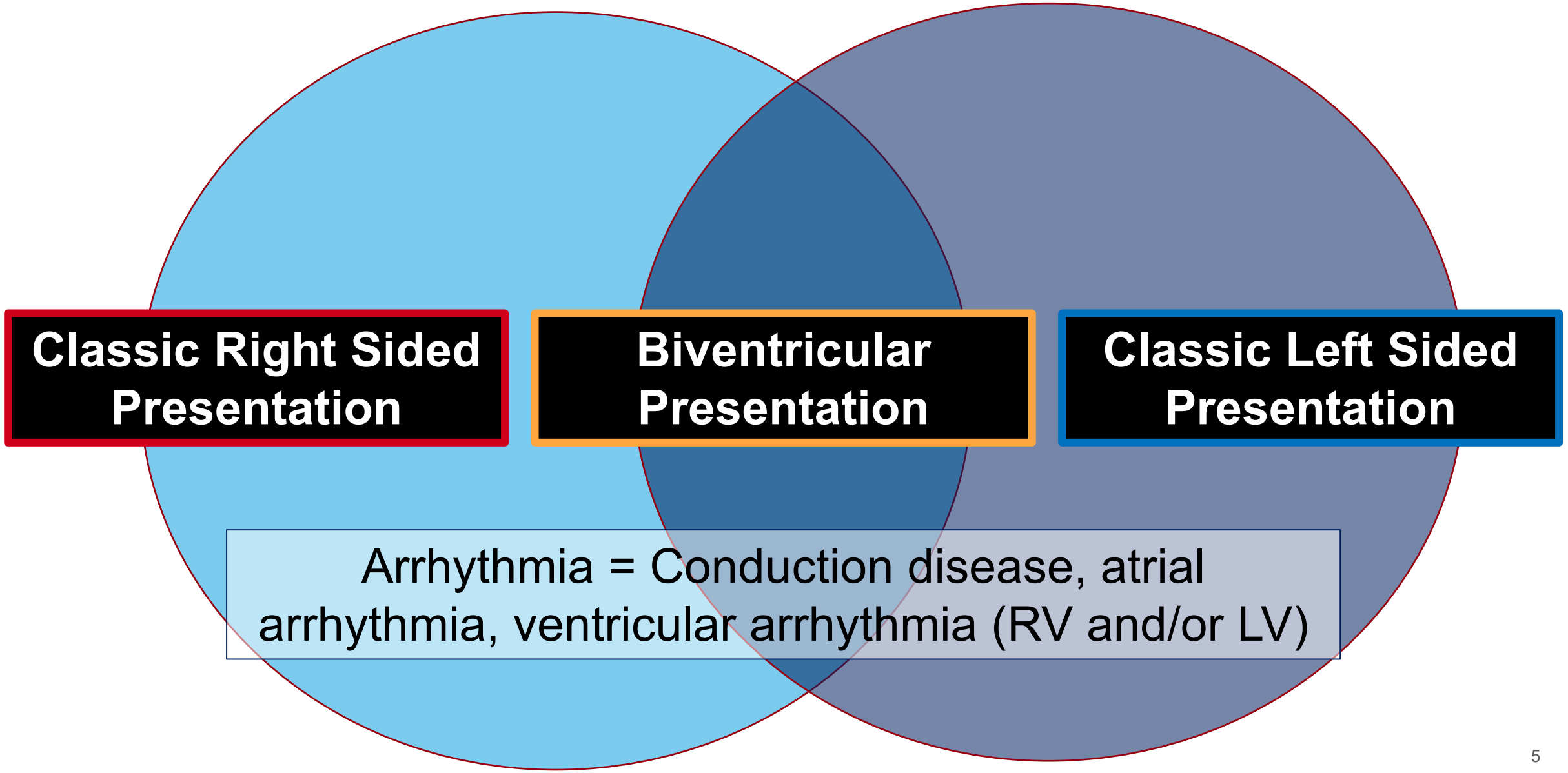
Disclosures

- Speaker/Honoraria for Medtronic, Abbott, Boston Scientific

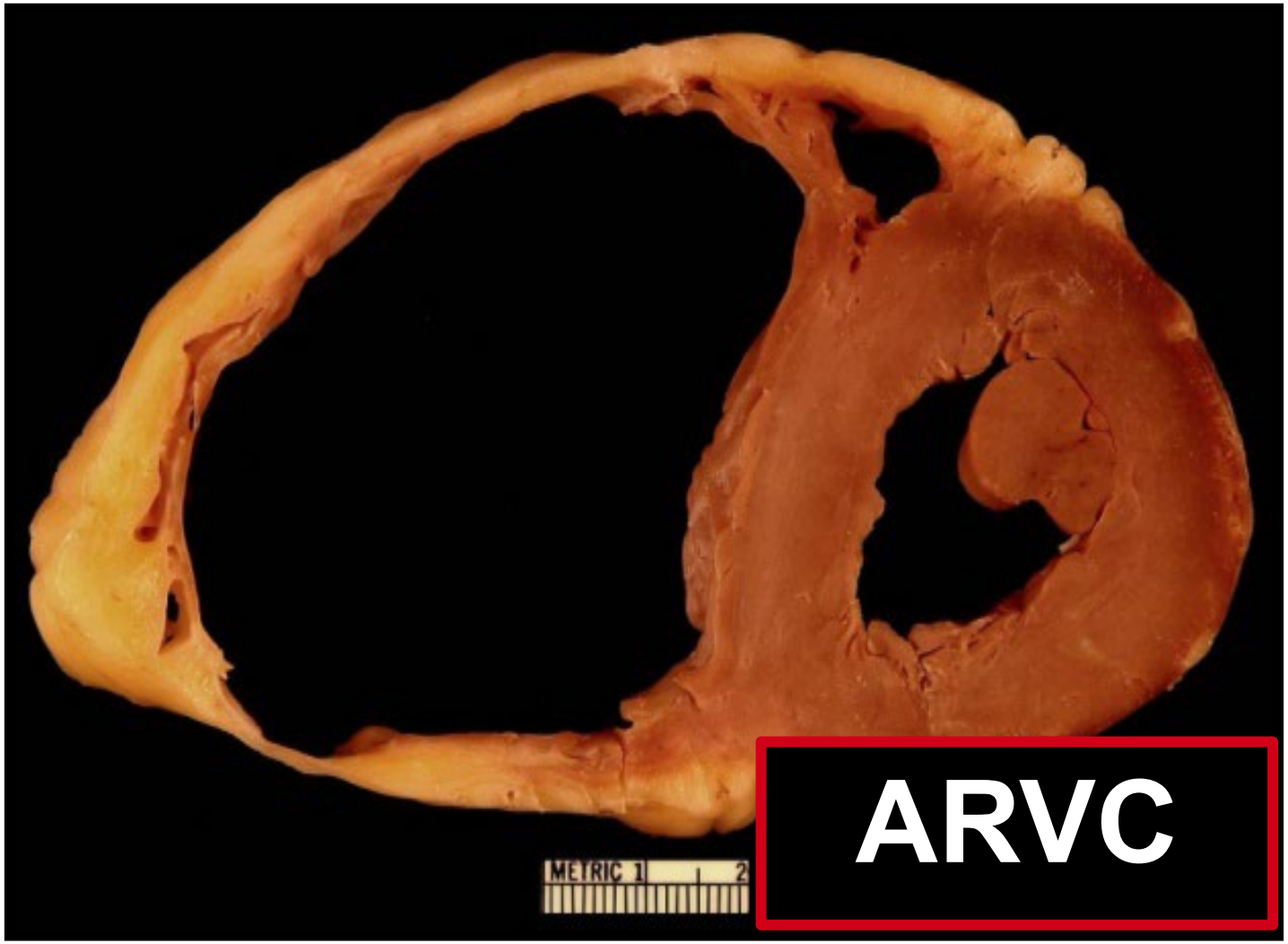
Learning Objectives

- Review the key clinical features of the arrhythmogenic cardiomyopathies
- Discuss the different genetic subtypes of ACM
- Identify the implications for clinical management of genetic testing results
- Recognize the impact that genetic testing can have on individual patient management
- Review who with ACM may need an ICD

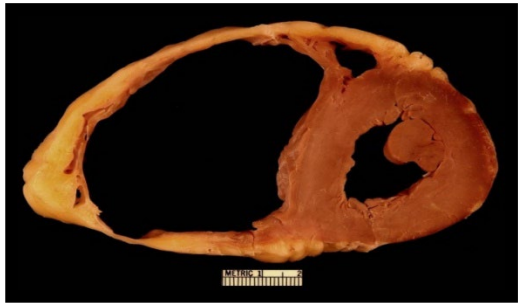
Genetic Arrhythmogenic Cardiomyopathy



Genetic Arrhythmogenic Cardiomyopathy



Arrhythmogenic Right Ventricular Cardiomyopathy



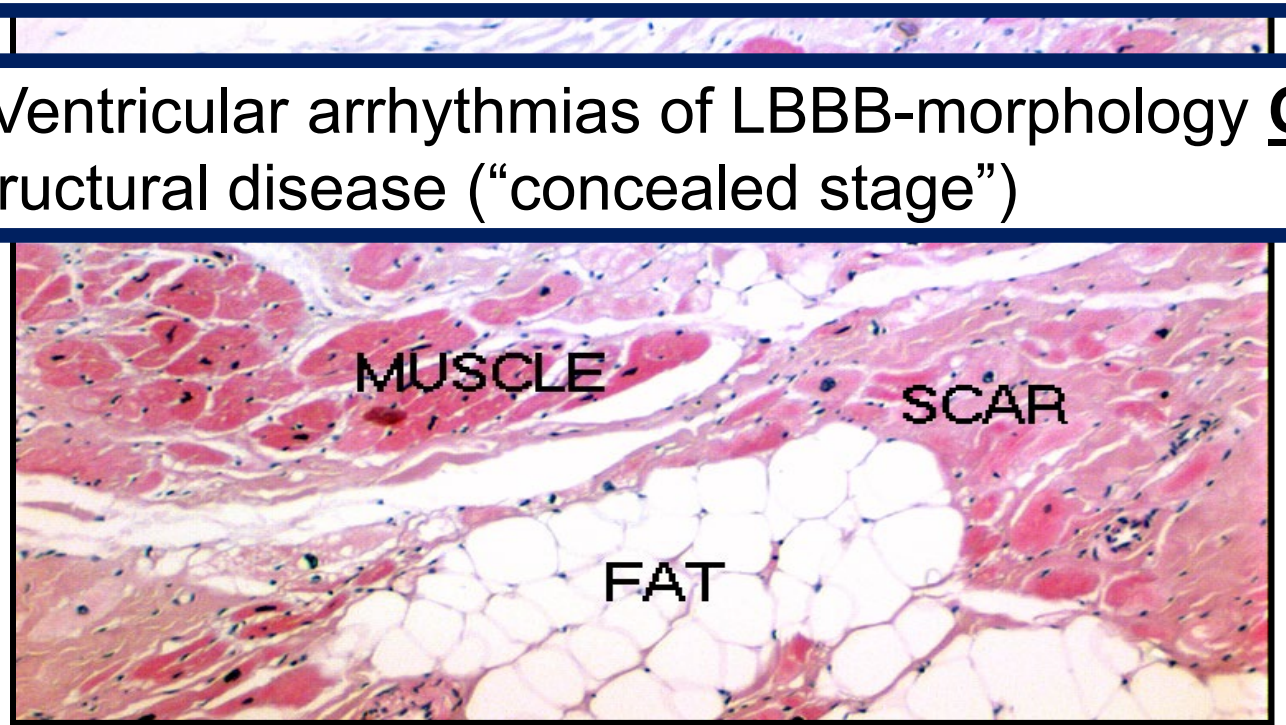
- Prevalence: 1:2000 – 1:5000
- Slight (55-60%) male predominance
- Age dependent penetrance (majority diagnosed between 2nd and 4th decades of life
- Predominant **RV INVOLVEMENT**
- Left bundle morphology **VENTRICULAR TACHYCARDIA**
- Replacement of the RV (+/- LV myocardium) with **FAT** and **FIBROSIS**
- Often familial with predominantly **AUTOSOMAL DOMINANT** inheritance
- "Classic ARVC" usually caused by variants encoding desmosomal proteins
- Internationally agreed upon guidelines for diagnosis

Arrhythmogenic Right Ventricular Cardiomyopathy

- Known incidences of ARVC account for 17% of all sudden deaths in young adults

- SCA is the initial manifestation of ARVC in 20-50% of cases

- Ventricular arrhythmias of LBBB-morphology **<u>OFTEN PRECEDE</u>** significant structural disease (“concealed stage”)



Clinical Approach to ARVC

ASSESSMENT

- History and pedigree
- ECG, SAECG, Holter
- Echo, MRI
- Genetic testing

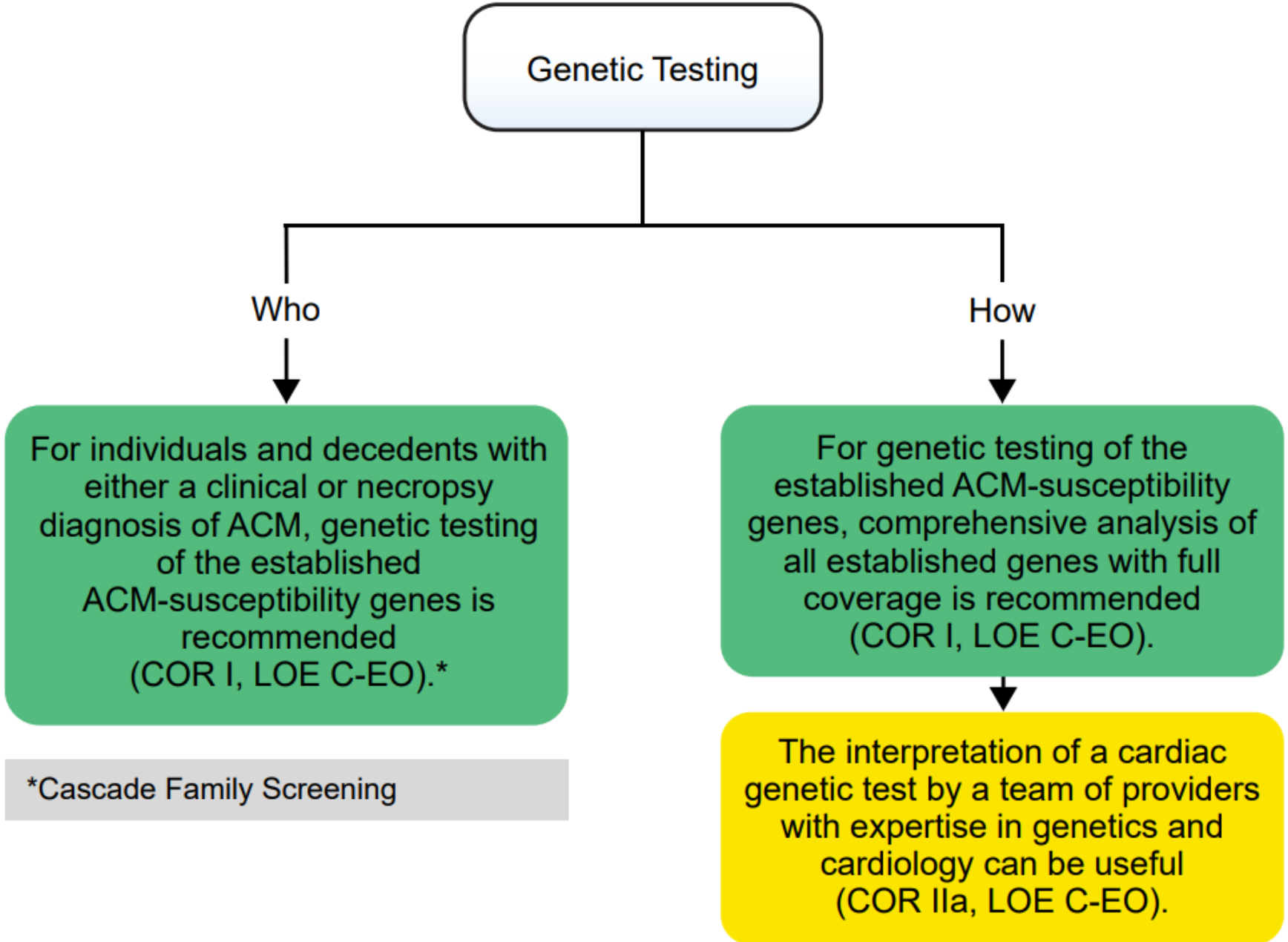
	MAJOR	MINOR
Global or regional dysfunction and structural alterations by echo, MRI or angiography		
Tissue characterization of wall (endomyocardial biopsy)		
Repolarization abnormalities (ECG)		
Depolarization abnormalities (ECG; SAECG)		
Arrhythmias		
Family History		
	First degree relative satisfying TFC	FDR with ARVC (cannot confirm TFC)
	Pathology confirmation at surgery or autopsy	Sudden death (<35) due to suspected ARVC in FDR
	Pathogenic mutation in patient under assessment	Pathology confirmation or TFC in second degree relative

Definite: 2 major or 1 major and 2 minor or 4 minor criteria from different categories
Borderline: 1 major and 1 minor or 3 minor criteria from different categories
Possible: 1 major or 2 minor criteria from different categories

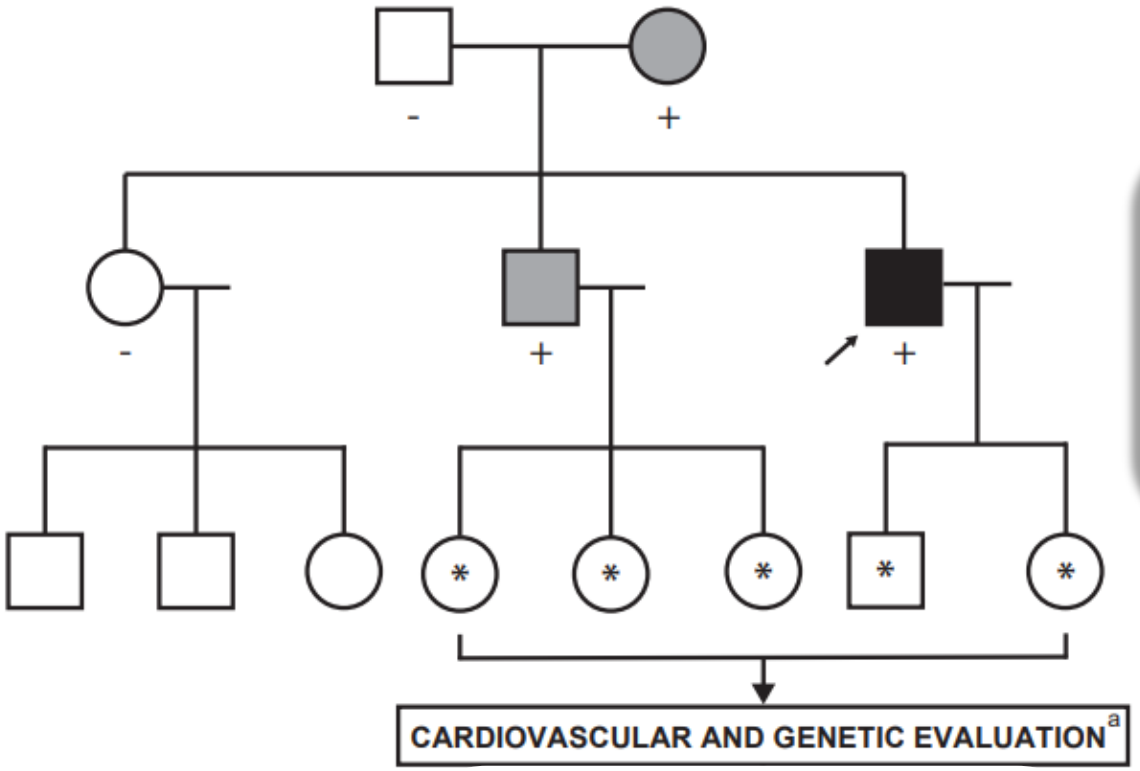
Genetics of ARVC

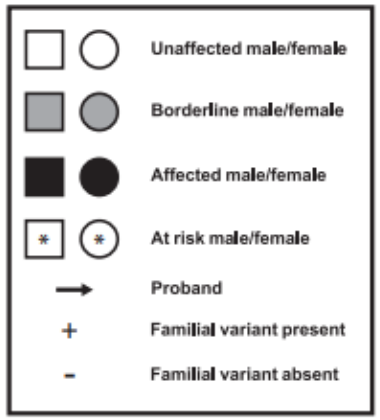
DESMOSOMAL GENES		NON-DESMOSOMAL GENES
• PKP2	(20 – 46%)	• TMEM43
• DSP	(10%)	• DES
• DSG2	(10%)	• PLN
• DSC2	(5%)	
• JUP	(<1%)	

- 2/3 of patients who fulfill ARVC diagnostic TFC have a causal variant
- 50-60% of ARVC is caused by variants affecting genes encoding desmosomal proteins


Genetic Testing
Who
How
For individuals and decedents with either a clinical or necropsy diagnosis of ACM, genetic testing of the established ACM-susceptibility genes is recommended (COR I, LOE C-EO).*
*Cascade Family Screening
For genetic testing of the established ACM-susceptibility genes, comprehensive analysis of all established genes with full coverage is recommended (COR I, LOE C-EO).
The interpretation of a cardiac genetic test by a team of providers with expertise in genetics and cardiology can be useful (COR IIa, LOE C-EO).

THREE-GENERATION PEDIGREE





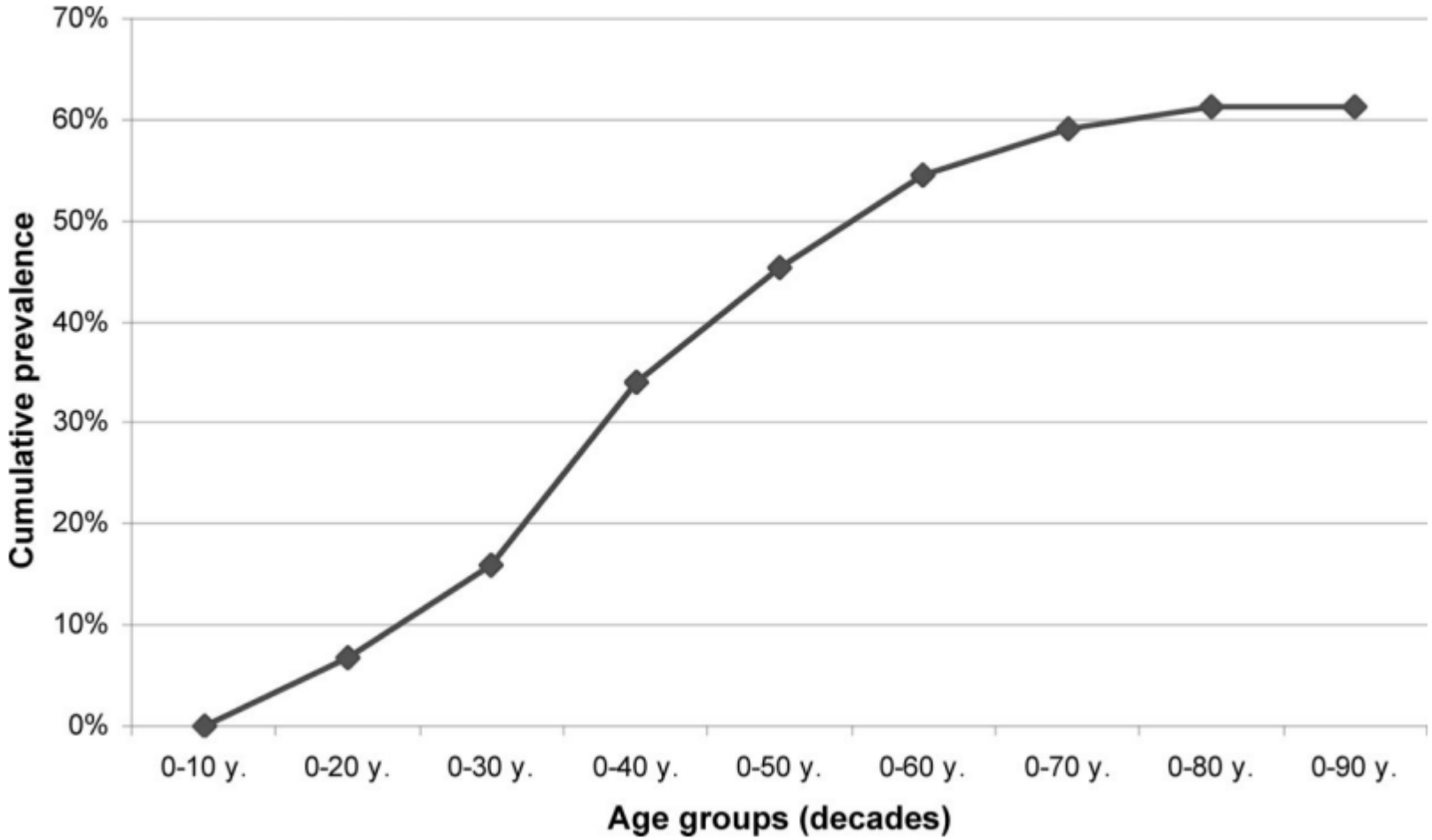
It is recommended that a genetic counselor or appropriately experienced clinician obtain a comprehensive 3-generation family history (COR I, LOEC-EO).

It is recommended that first-degree relatives undergo clinical evaluation every 1–3 years[b] starting at 10–12 years of age[c] (COR I, LOE B-NR).

Cardiovascular evaluation should include 12-lead ECG, ambulatory ECG, and cardiac imaging (COR I, LOE B-NR).

Exercise stress testing (arrhythmia provocation) may be considered as a useful adjunct to cardiovascular evaluation (COR IIb, LOE C-LD).

a. The use of genetic testing assumes prior identification of a pathogenic variant in the proband.
b. May vary with age, lifestyle, and family history.
c. Unless family history of disease suggests potential for earlier onset or presence of pathogenic variant in family supports presymptomatic genetic testing.



Cumulative proportion by age of penetrant disease among gene positive first-degree relatives

Quarta et al. Circulation. 2011;123:2701-2709.

Do the Genetics Really Matter in ACM?

- Pathogenic PKP2 variants: most common cause of ACM in North America
- PKP2 ACM typically presents as **"classic ARVC"**

More likely to fit the **2010 Task Force Criteria**

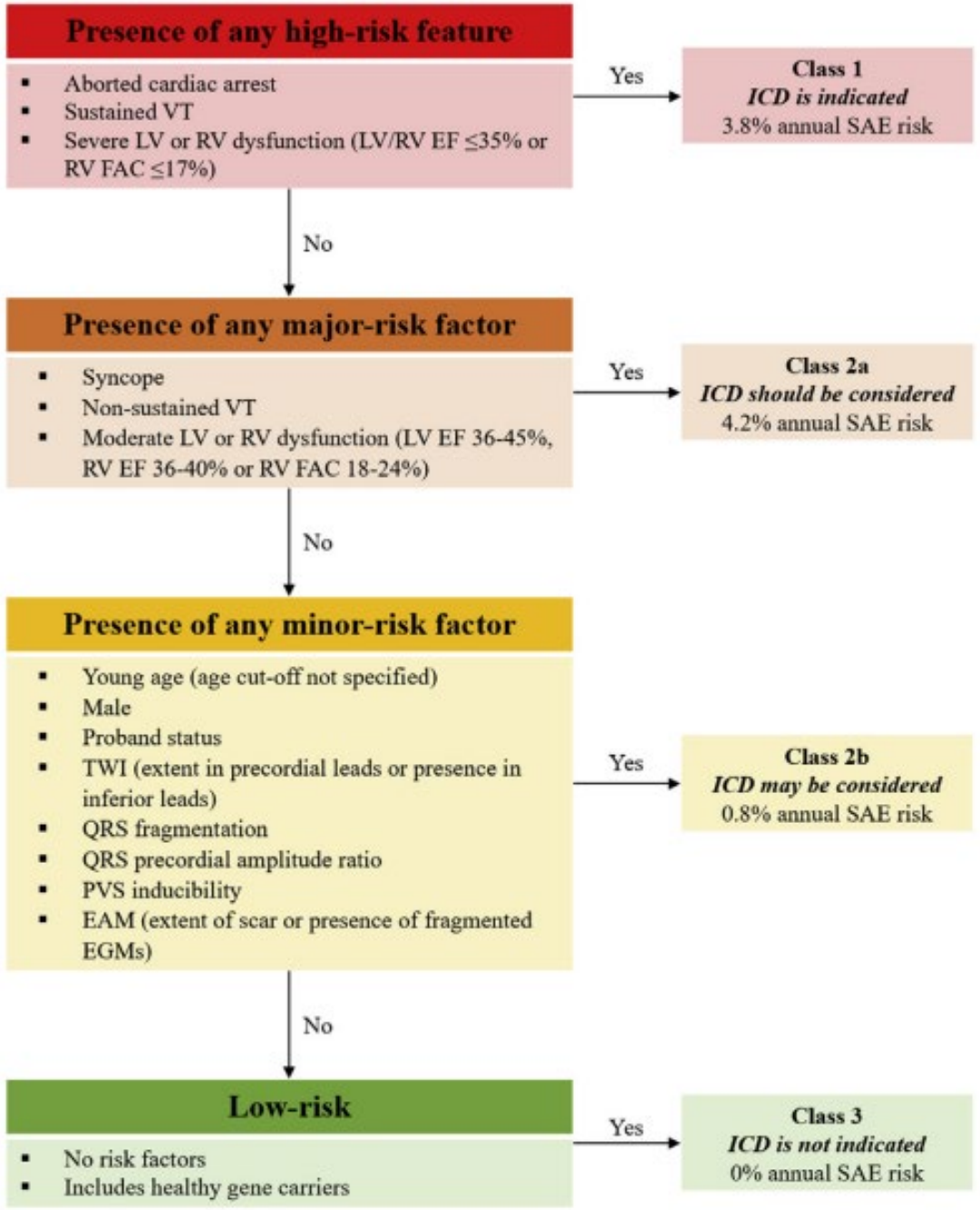
- Precordial T wave inversion
- LBB VT
- RV dyskinesis
- Clear correlation between vigorous (esp. endurance) exercise and disease penetrance and progression

There may be specific management considerations "
for a specific genetic substrate

ARVC Risk Stratification

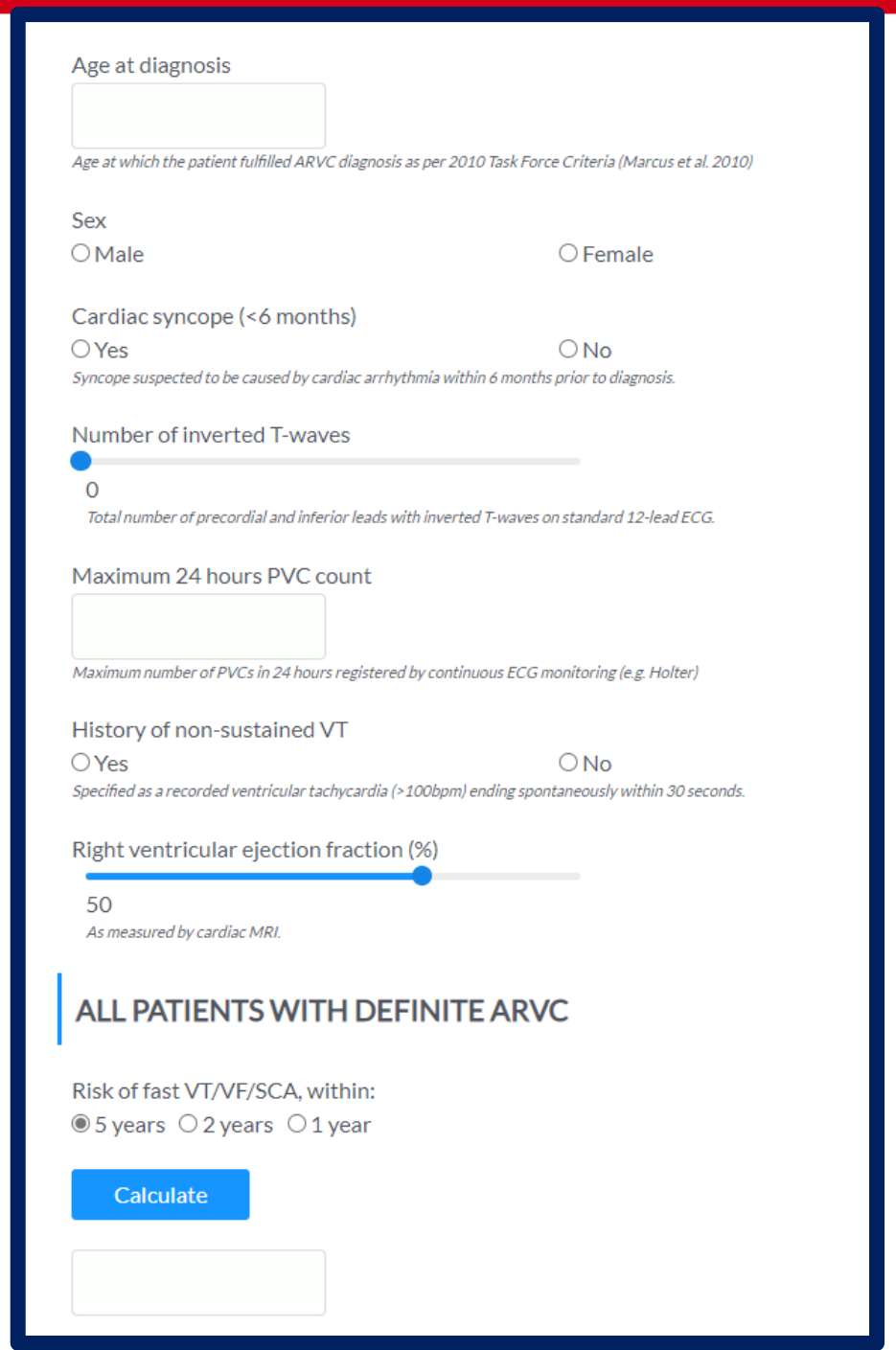
ESTABLISHED MARKERS

- Cardiac arrest
- Ventricular tachycardia
- Age
- Male sex
- Cardiogenic syncope
- Extent of TWI
- PVC count
- Reduced LV/RV function



ARVCRISK.COM

Estimates the risk of ventricular arrhythmias within 5 years for patients with *definite* ARVC (primary prevention patients only)



Do the Genetics Really Matter?

ARVC PREDOMINANT

Biventricular Presentation

ALVC PREDOMINANT

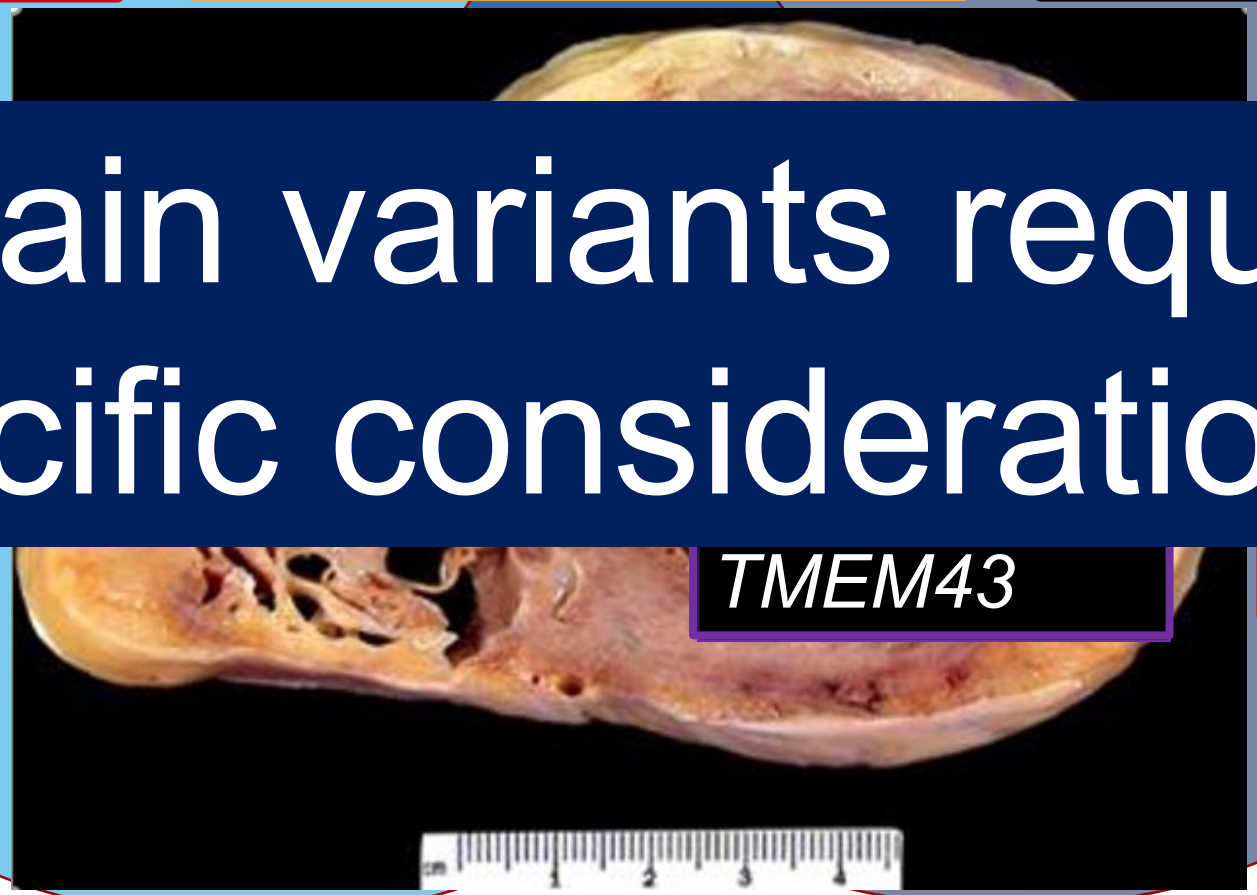
DSG2

DSC2

JUP

TMEM43

RBM20



Certain variants require specific considerations

CASE: A Wolf in Sheep's Clothing?

20-year-old presents for evaluation of **recurrent myocarditis**

"How worried are you about this problem?"

PATIENT **"Not at all"**

MOM **"Really worried"**

A Wolf in Sheep's Clothing

20-year-old presents for evaluation of **recurrent myocarditis**

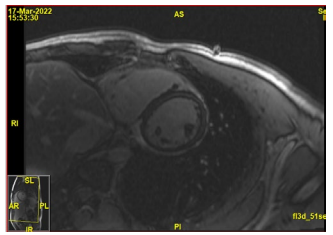
8/2017

VIRAL MYOCARDITIS

Chest pain
Troponin +++

Colchicine
NSAIDS

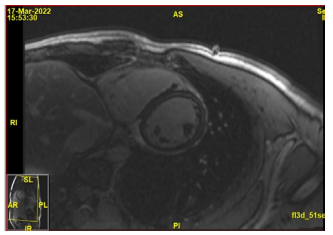
MRI:
Extensive edema,
LGE
Hypokinesis (EF 58%)



1/2022

Chest pain
Troponin +++

MRI:
Extensive edema
LGE
Hypokinesis



6/2022

First negative troponin

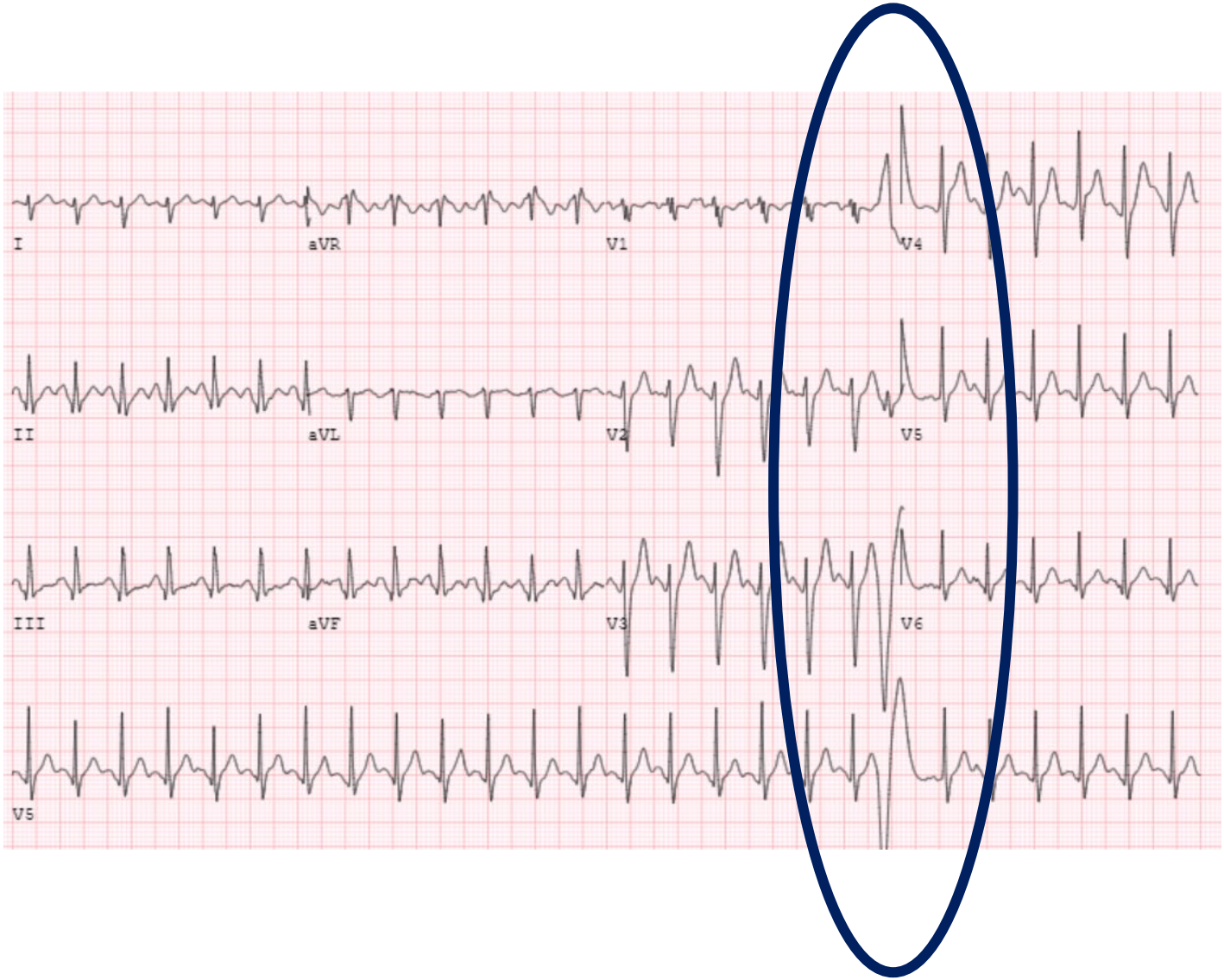
Now What?

- Dismiss
- Holter
- Stress test
- Genetic Testing
- ICD

Testing

<u>24 Hour Holter</u>:
Sinus rhythm
(41 – 111); PVCs (780)

<u>ECHO</u>:
Mild LV enlargement
No RWMA
LVEF 55%
Borderline enlarged RV
Normal RVEF



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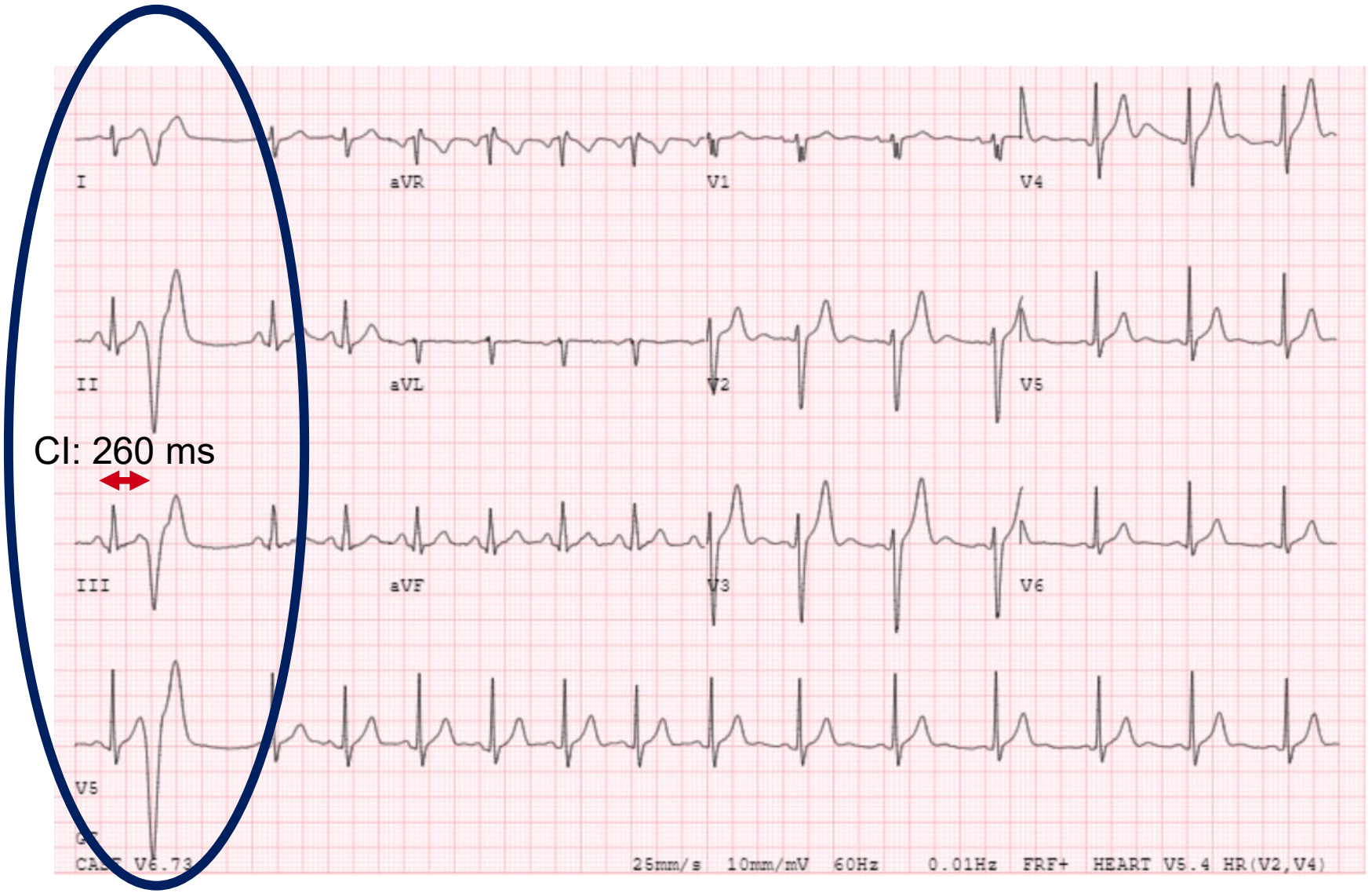
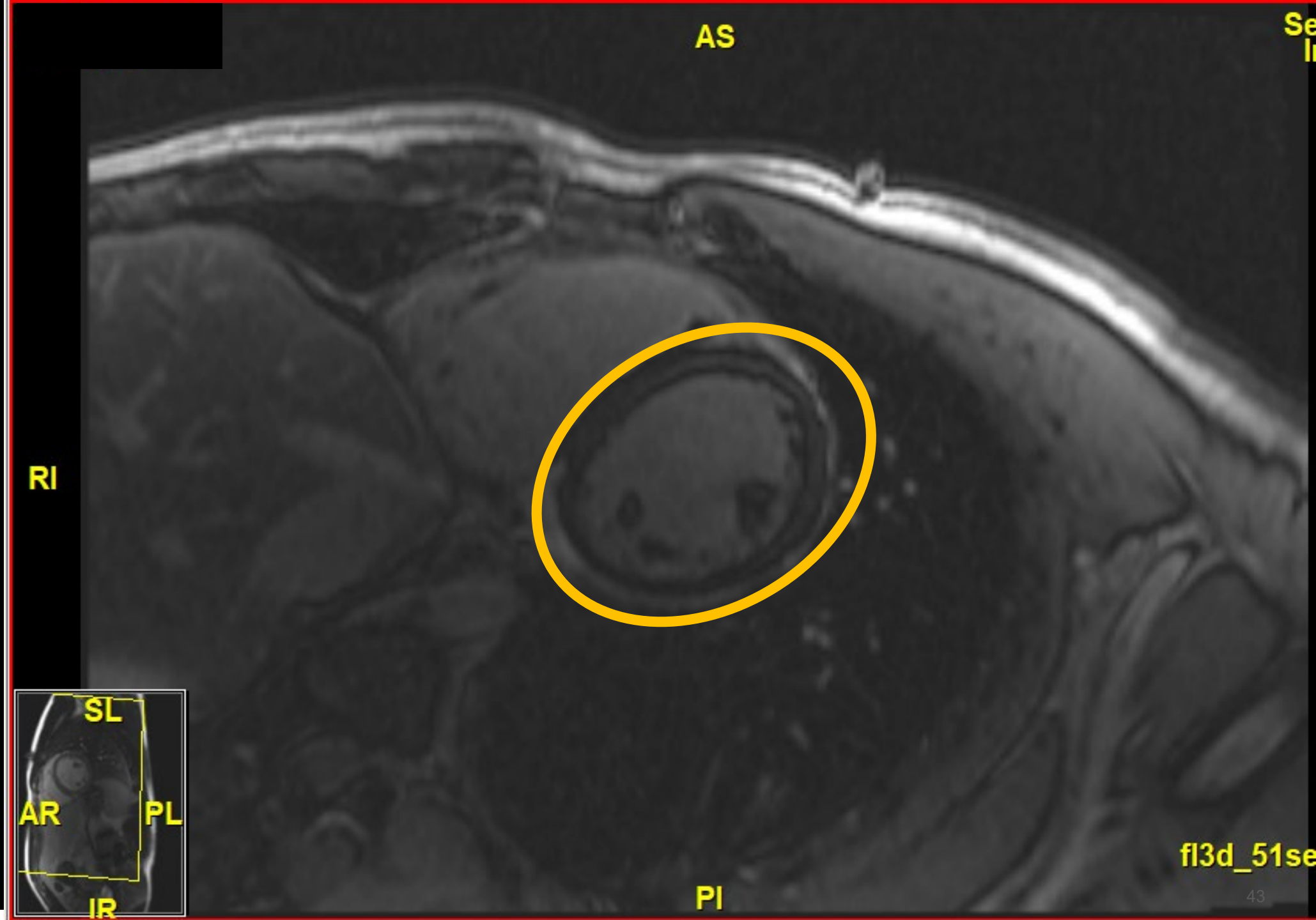


CARDIAC MRI

Ring like LGE



Now What?

DSP c.6496C>T
(p.Arg2166Ter)

Pathogenic

Now What?

- Dismiss
- Monitor for LV dysfunction
- ICD

Desmoplakin Mediated ACM

CLINICAL FEATURES

- Episodes of chest pain/recurrent myocardial injury (positive troponin)
- PET may be positive!
- “Ring like” subepicardial LGE (precedes LV systolic dysfunction)

PHENOTYPE IS KEY

IT FITS!!!!

Desmoplakin Mediated ACM

CLINICAL FEATURES

- Episodes of chest pain/recurrent myocardial inju (positive troponin)
- PET may be positive!
- "Ring like" subepicardial L (precedes LV systolic dysfu

AN ICD IS REASONABLE IF:

LVEF < 55%

pecially if:

nt PVCs

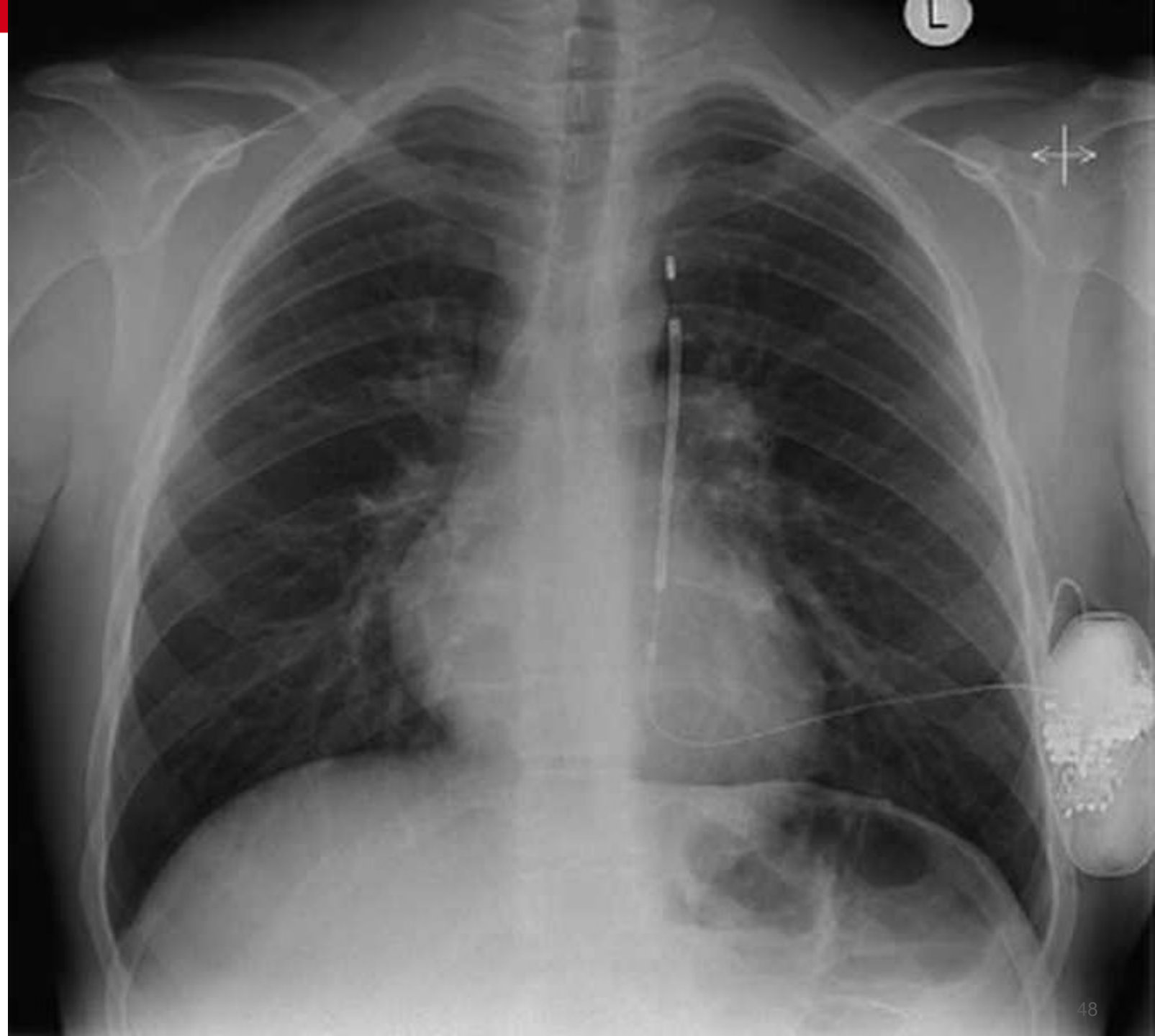
LV LGE

FREQUENT (>500/24h) SHORT COUPLED

EXTENSIVE "RING LIKE"

PRIMARY PREVENTION ICD IMPLANTED

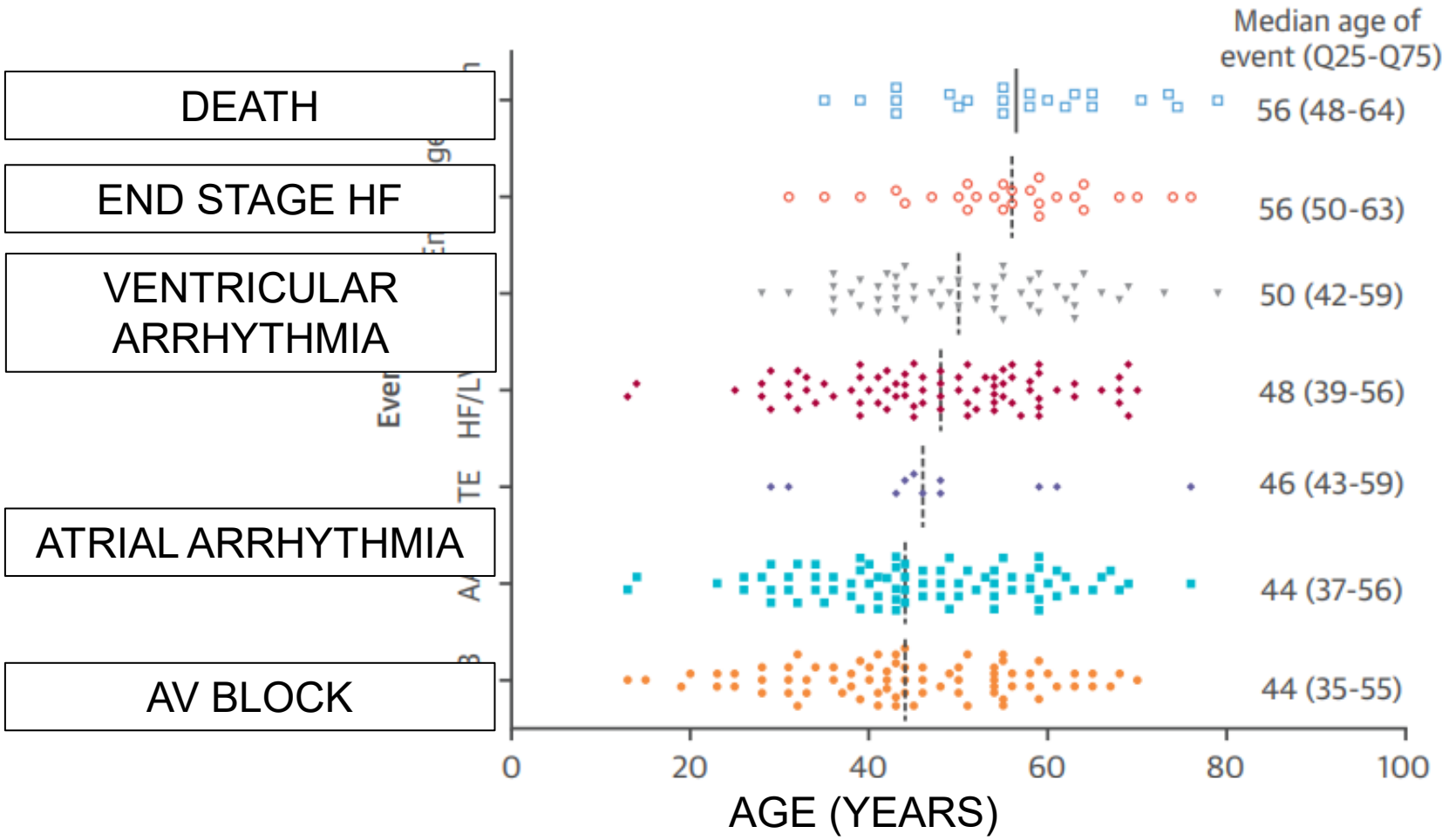
CASCADE FAMILY SCREENING ONGOING



LMNA

CLINICAL FEATURES

- Atrial arrhythmia
- Conduction system disease
- Ventricular arrhythmia
- LV systolic dysfunction



The median age at which clinical events occurred demonstrated a stepwise increment as disease intensified. AA = atrial arrhythmia; AVB = atrioventricular block; HF = heart failure; LVD = left ventricular dysfunction; TE = thromboembolism; VA = ventricular arrhythmia.

Kumar…MacIntyre…Lakdawala.. JACC. 2016.

LMNA

CLINICAL FEATURES

- Atrial arrhythmia
- Conduction system disease
- Ventricular arrhythmia
- LV systolic dysfunction

AN ICD IS REASONABLE IF **2 or MORE** OF THE FOLLOWING:

LVEF < 45%

NSVT

Male Sex

OR

Pacing indication

FLNC

CLINICAL FEATURES

- Biventricular cardiomyopathy (but LEFT dominant most common)
- High arrhythmia risk
- Extensive subepicardial LGE
- Low voltage ECG
- Inferolateral or lateral TWI (common)

RISK FACTORS FOR SUDDEN DEATH

T wave inversion

LGE on MRI

NOT

LV dilation

LV systolic dysfunction

FLNC

CLINICAL FEATURES

- Biventricular cardiomyopathy (but LEFT dominant most common)
- High arrhythmia risk
- Extensive subepicardial LGE
- Low voltage ECG
- Inferolateral or lateral TWI (common)

A PRIMARY PREVENTION ICD IS REASONABLE IF:

LVEF < 45%

PLN

CLINICAL FEATURES

- Low voltage ECG
- Ventricular arrhythmias (+++)
- Biventricular heart failure
- Progression to end stage heart failure

RISK FACTORS FOR SUDDEN DEATH

T wave inversion

LGE on MRI

NOT

LV dilation

LV systolic dysfunction

PLN

CLINICAL FEATURES

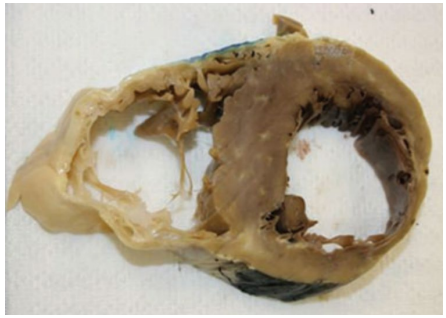
- Low voltage ECG
- Ventricular arrhythmias (+++)
- Biventricular heart failure
- Progression to end stage heart failure

AN ICD IS REASONABLE IF:

LVEF < 45%

NSVT

TMEM43 p.S358L



- Very penetrant and very arrhythmic
- High mortality
- Males >>> Females
- Poor R wave progression
- (2 x more likely in males)
- LV dilation/heart failure
- Ventricular ectopy occurs early
- ICD in variant positive post pubertal males as PP

What about “Genome first” diagnosis

- Expansive genetic testing is more widely available
- Almost all ACM genes are “reportable” secondary findings
- Rising number of incidental findings in ACM genes

CAUTION!

Remember:

REDUCED penetrance

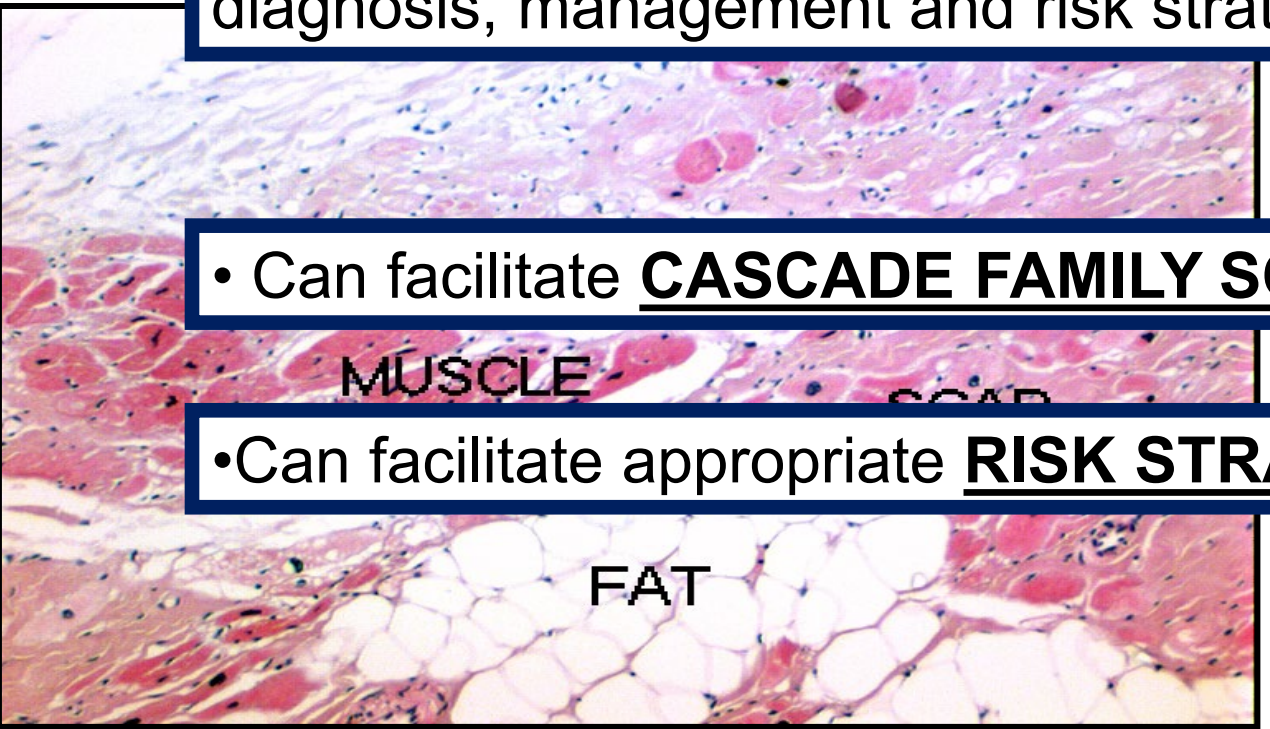
Often NO family history

Often NO clinical story

Arrhythmogenic Cardiomyopathy: Future Is Now?

- The era of precision – medicine is now

- Genetic counseling and testing is strongly recommended as part of the diagnosis, management and risk stratification of patients with ACM



- Can facilitate **CASCADE FAMILY SCREENING**

- Can facilitate appropriate **RISK STRATIFICATION** (one size does not fit all)

Q&A Period

THANK YOU!

Please remember to complete the session evaluation

Next Up! Please make your way down to the *Exhibit Hall (Samuel ABC) for a Health Break* and then proceed to the *Champlain Ballroom for Plenary 2 Clinical Pearls and Conundrums in HF Clinical Care* beginning at 3:00 pm.