PERSONALIZED RISK ASSESSMENT IN HCM: LIFETIME SUDDEN DEATH AND HEART FAILURE RISK

A Collaborative Approach to Hypertrophic Cardiomyopathy

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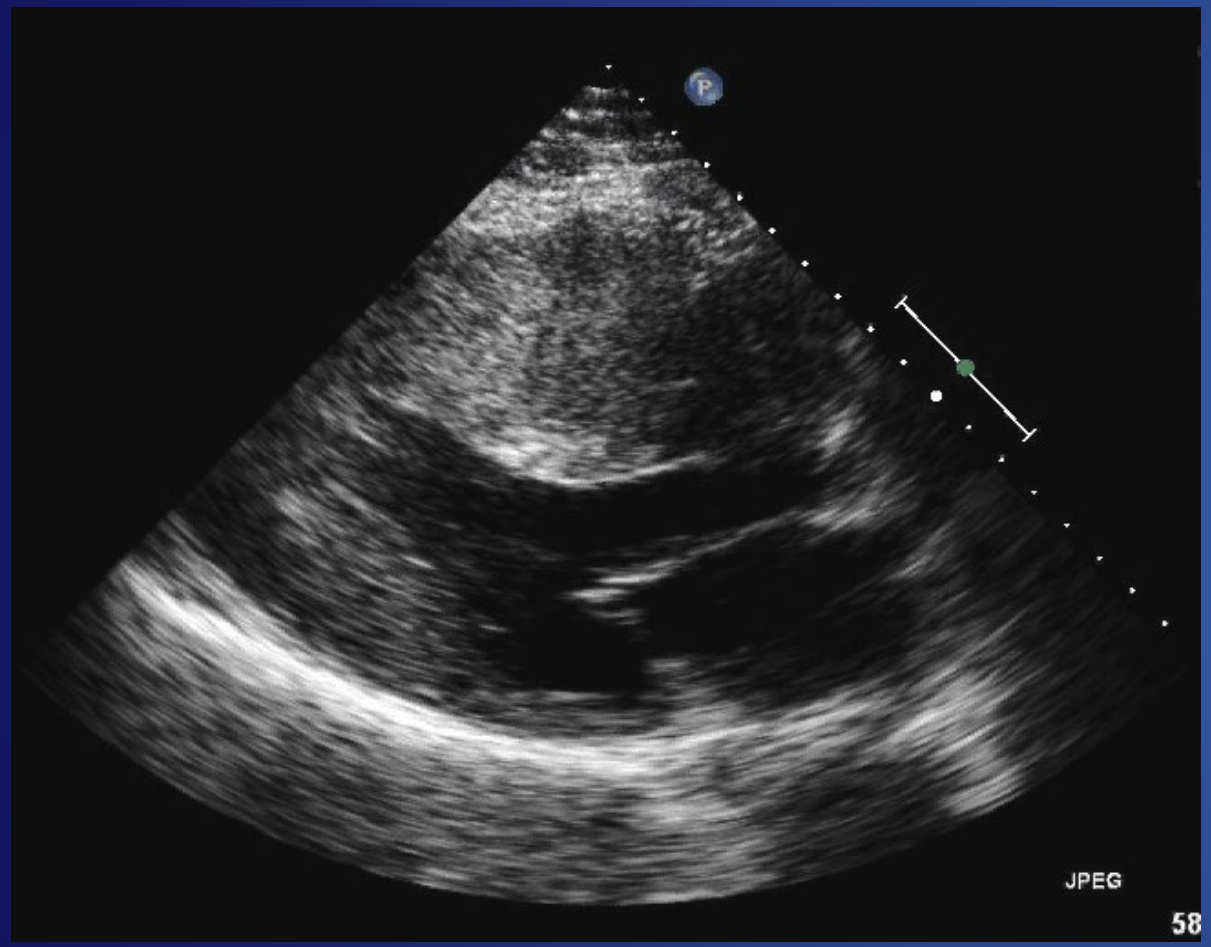
OUTLINE

1. Case Presentations
2. Familial versus Non-Familial HCM
3. Impact of Genetic Testing on Lifetime Risk
4. SCD Risk Prediction
5. Heart Failure Risk Prediction

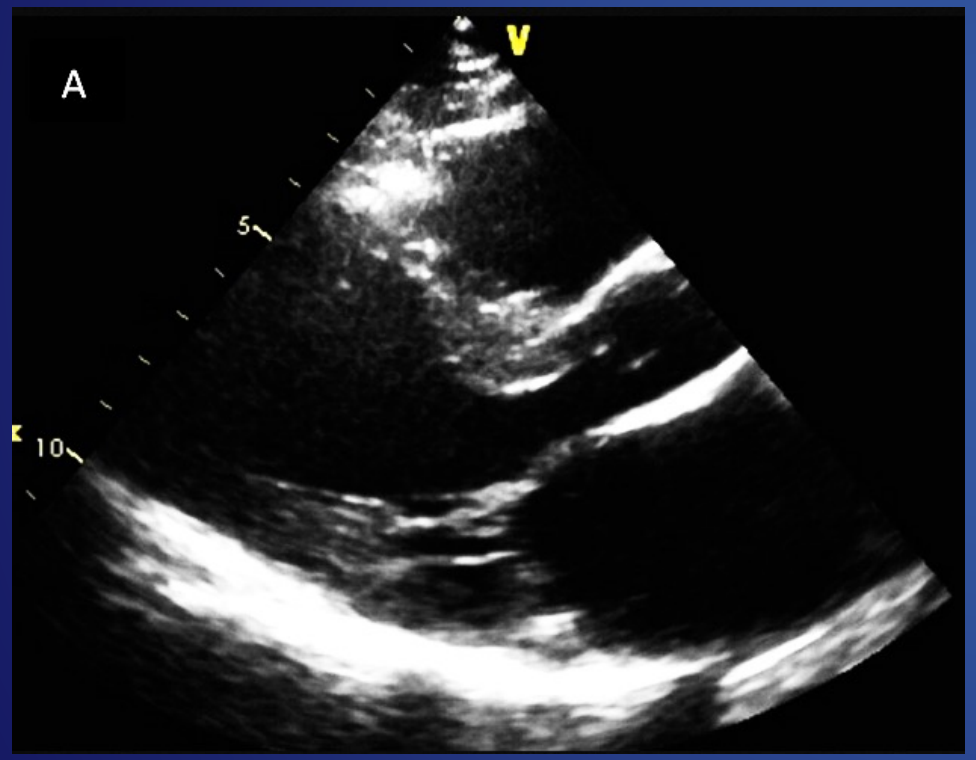
CASE 1: EARLY ONSET HCM DUE TO A SARCOMERE GENE MUTATION



Echo at Age 26

Age	
23	HCM Diagnosed, hypertrophy throughout septum (reverse curve)
24	ICD implanted
25	LVOT obstruction treated with myectomy
28	Appropriate shock
34	Diuretic-requiring heart failure
36	Atrial fibrillation, further complicating heart failure

CASE 2: LATE AGE PRESENTATION HCM WITH NEGATIVE GENETIC TESTING



Age

65 HCM Diagnosed, hypertrophy primarily at basilar septum

66 LVOT obstruction treated with myectomy

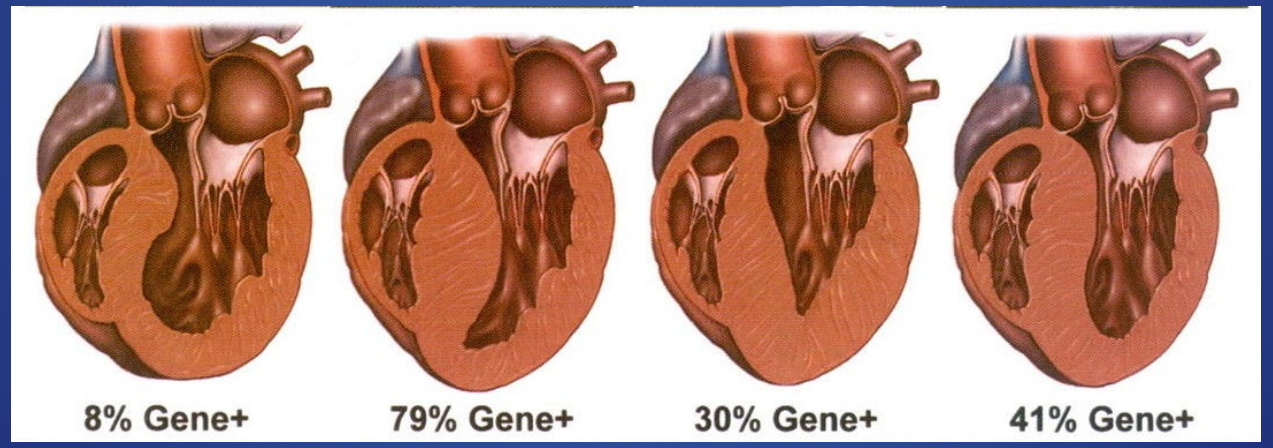
73 Atrial fibrillation, managed medically

76 Doing well

HCM: LIKELIHOOD OF + GENETIC TEST IS DETERMINED BY CLINICAL PROFILE

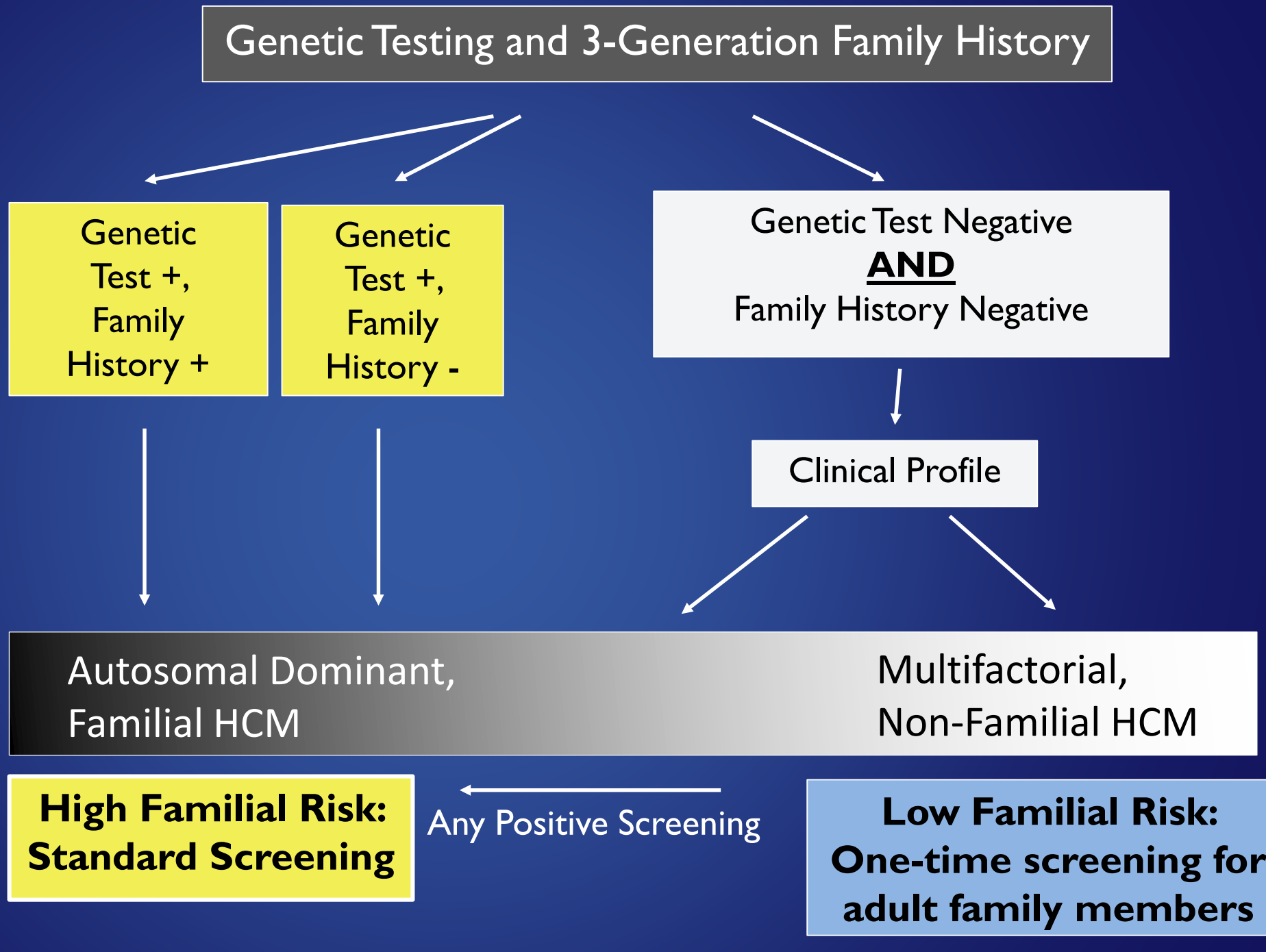
- Earlier age of diagnosis
- Family history of HCM
- Lack of hypertension
- Morphology of hypertrophy

Positive Genetic Test

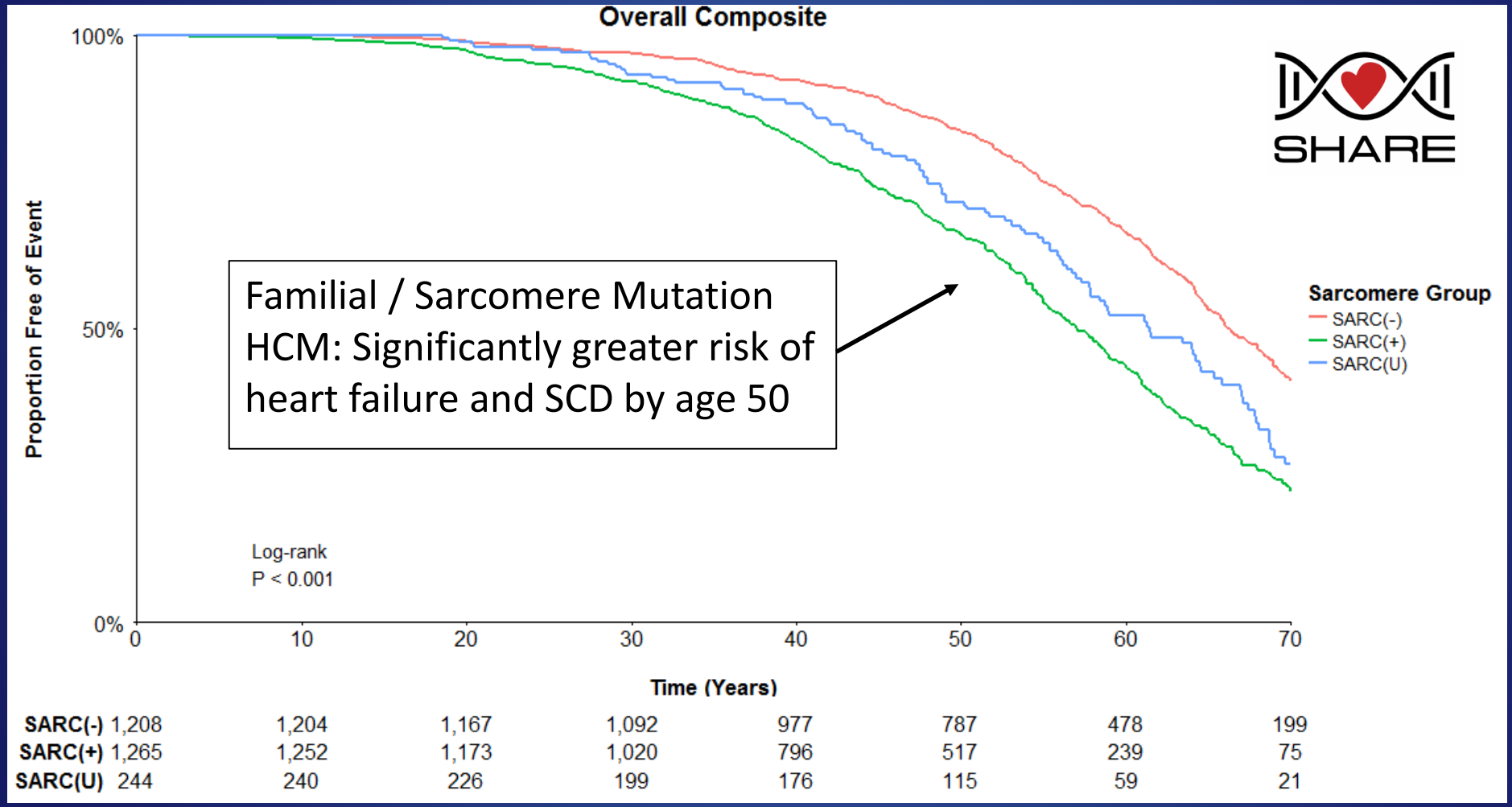


Binder, Ommen, et al., *Mayo Clinic Proc* 2006
Gruner, et al., *Circ Cardiovasc Genet* 2013
Ko, et al., Genetics in Medicine 2017

Michigan Experience:
Yield of familial screening with negative genetic testing and negative family history is very low.
Ko, et al. 2017,
Genetics in Medicine



FAMILIAL (SARCOMERE GENE POSITIVE) HCM → MORE ADVERSE EVENTS AT YOUNGER AGE



Ho, et al., *Circ* 2018

FAMILIAL VS. NON-FAMILIAL HCM KEY POINTS

- HCM can be generally divided into Familial HCM and Non-Familial HCM
- Familial HCM is identified by a combination of
  - Clinical features: earlier onset, LVH morphology, lack of HTN
  - Family history (but a negative FamHx does NOT rule out familial HCM)
  - Genetic testing
- Screening efforts should be focused on family members of individuals with higher likelihood of Familial HCM

SUDDEN DEATH RISK ASSESSMENT IN HCM

- Traditional Risk Factors
  - Max wall >30 mm, NSVT (> 3 beats, > 120 bpm), family hx of early (<40 yo) sudden death, syncope, ~~abnormal blood pressure response to exercise~~
- European Society of Cardiology (ESC) HCM Risk Estimate
  - Adds age-weighting for greater risk at younger age
  - Adds left atrial size
  - Adds max wall thickness as a continuous variable
  - Adds LVOT gradient
  - Removes blood pressure response
  - *Does not include genetics or MRI*

ESC Risk Calculator:
Google: "ESC HCM risk"

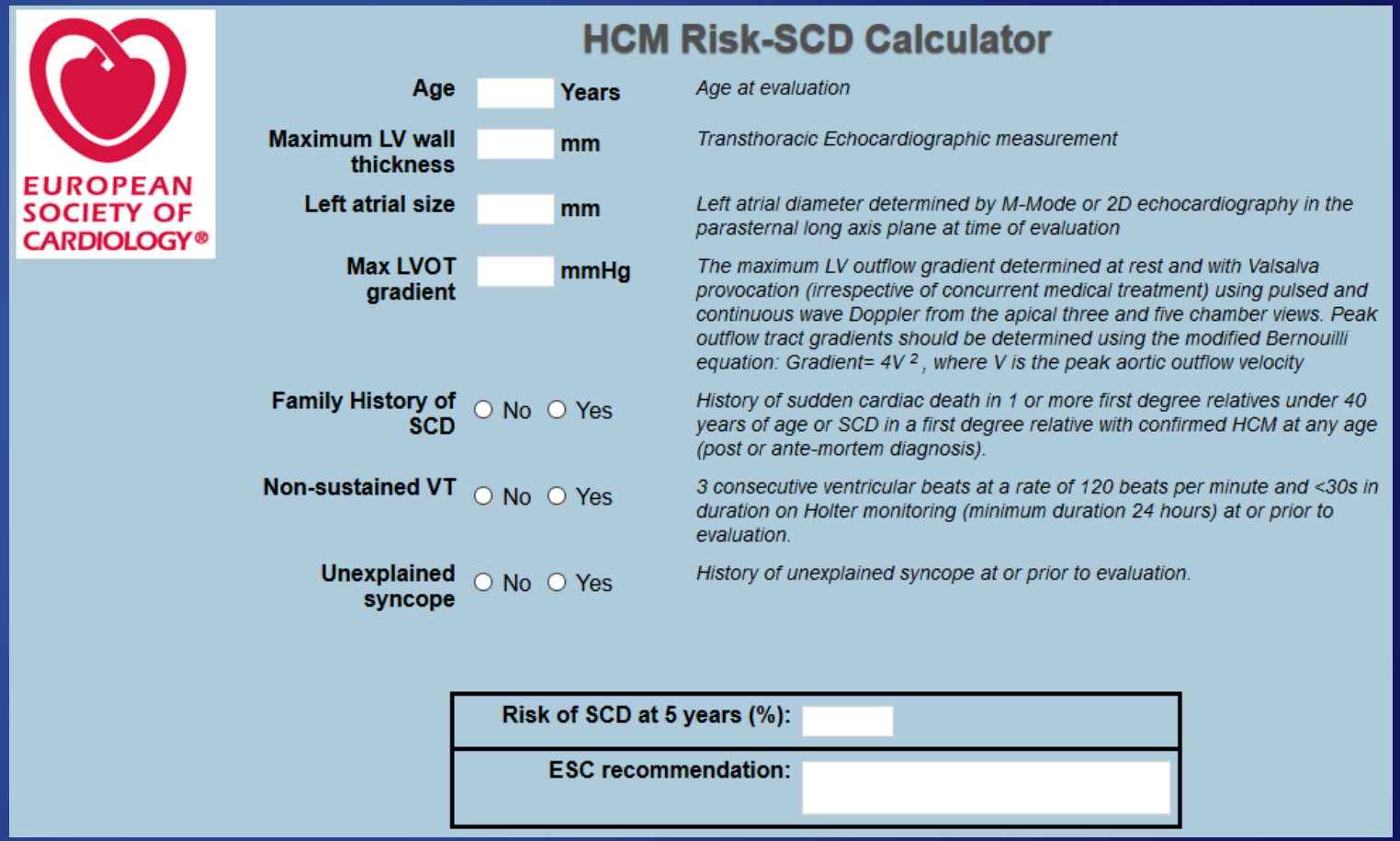
O'Mahony, et al., *EHJ* 2014

SUDDEN DEATH RISK ASSESSMENT IN HCM: CASE 1

70 yo with HCM, sigmoidal septal hypertrophy, LVOT obstruction with 60 mm Hg gradient, max thickness 19 mm, LA 46 mm

- 5-year risk = 1.7%
- If NSVT = 3.9%

Strategy: Yearly follow-up, minimal rhythm monitoring, MRI only if septal reduction planned



Google: "HCM ESC risk"

O'Mahony, et al., *EHJ* 2014

SUDDEN DEATH RISK ASSESSMENT IN HCM: CASE 2

20 yo with HCM, reverse curve septal hypertrophy, no obstruction, max thickness 19 mm

- 5-year risk = 2.9%
- Risk by age 40 = 11.6%
- If NSVT = 6.4%

Strategy: Yearly follow-up, extended event monitoring yearly, MRI, advice on warning symptoms

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HCM Risk-SCD Calculator

Age	**Years**	*Age at evaluation*
Maximum LV wall thickness	**mm**	*Transthoracic Echocardiographic measurement*
Left atrial size	**mm**	*Left atrial diameter determined by M-Mode or 2D echocardiography in the parasternal long axis plane at time of evaluation*
Max LVOT gradient	**mmHg**	*The maximum LV outflow gradient determined at rest and with Valsalva provocation (irrespective of concurrent medical treatment) using pulsed and continuous wave Doppler from the apical three and five chamber views. Peak outflow tract gradients should be determined using the modified Bernouilli equation: Gradient= $4V^2$, where V is the peak aortic outflow velocity*
Family History of SCD	○ No ○ Yes	*History of sudden cardiac death in 1 or more first degree relatives under 40 years of age or SCD in a first degree relative with confirmed HCM at any age (post or ante-mortem diagnosis).*
Non-sustained VT	○ No ○ Yes	*3 consecutive ventricular beats at a rate of 120 beats per minute and <30s in duration on Holter monitoring (minimum duration 24 hours) at or prior to evaluation.*
Unexplained syncope	○ No ○ Yes	*History of unexplained syncope at or prior to evaluation.*

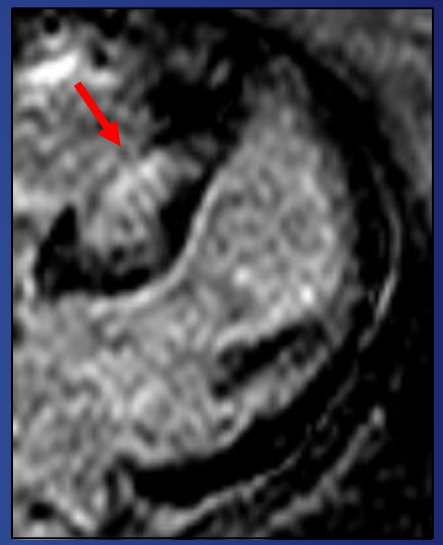
Risk of SCD at 5 years (%):	
ESC recommendation:	

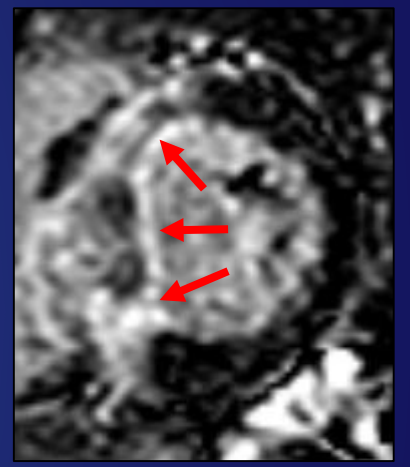
Google: "HCM ESC risk"

O'Mahony, et al., *EHJ* 2014

SCD ASSESSMENT: ADDITIONAL CONSIDERATIONS

- ESC risk calculator does not include genetic testing
  - Positive genetic test → MRI, longer rhythm monitoring
- ESC risk calculator does not include MRI LGE
  - MRI if intermediate risk and/or young sarcomere + patients with LVH >15 mm
  - Substantial marked LGE → likely high risk
- ESC risk calculator gives blanket recommendations for ICD based on 5-yr estimate
  - Young patients → higher lifetime burden of risk
- ESC risk calculator does not include HCM with apical aneurysm → high risk regardless of other variables



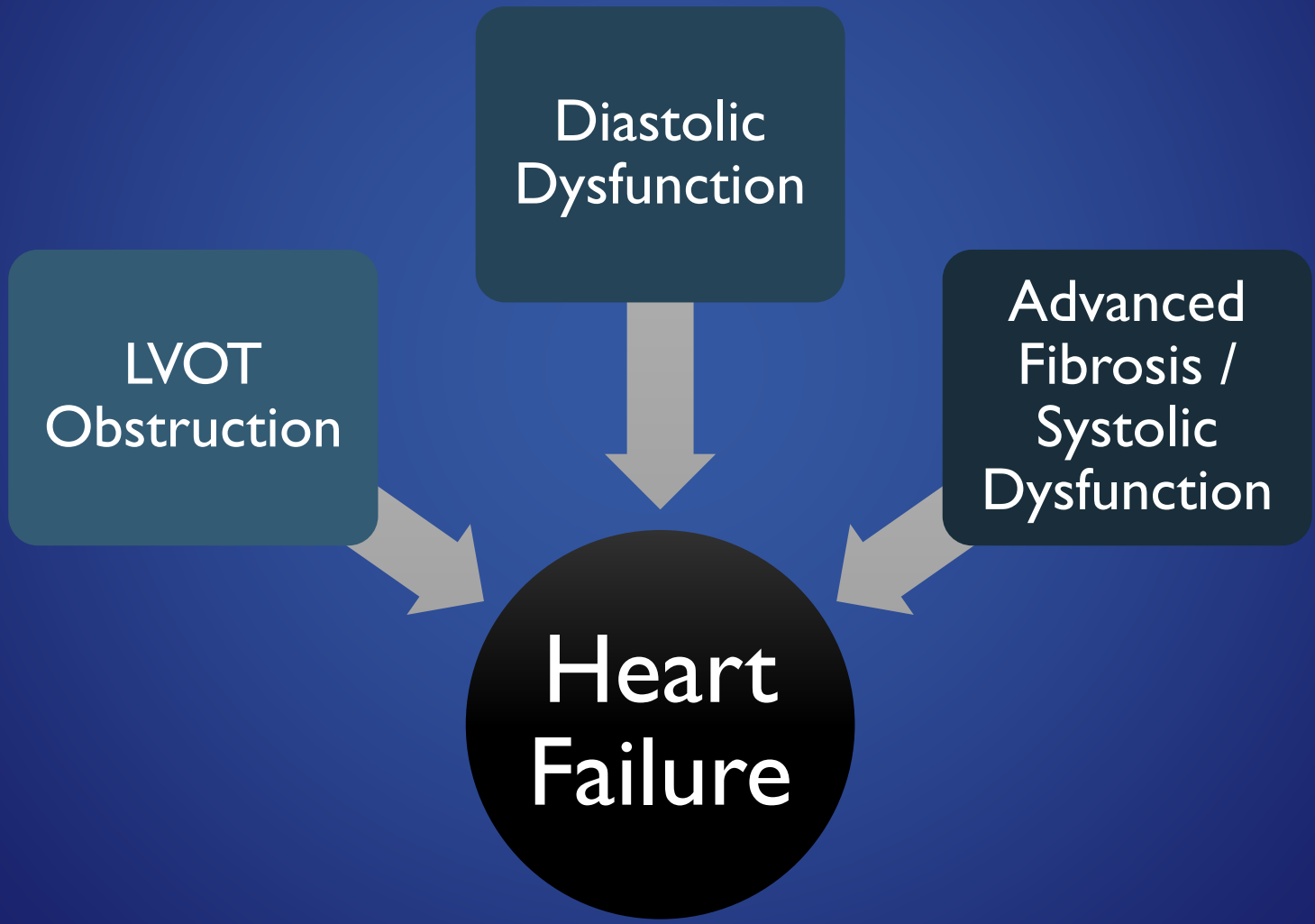


40 yo with *MYBPC3* mutation, nonobstructive HCM, max LVT 20 mm, LA 50 mm, ESC risk: 2.7%

MRI: Dense LGE in septum

UM Risk Estimate: High

HETEROGENEITY OF HEART FAILURE TYPES IN HCM

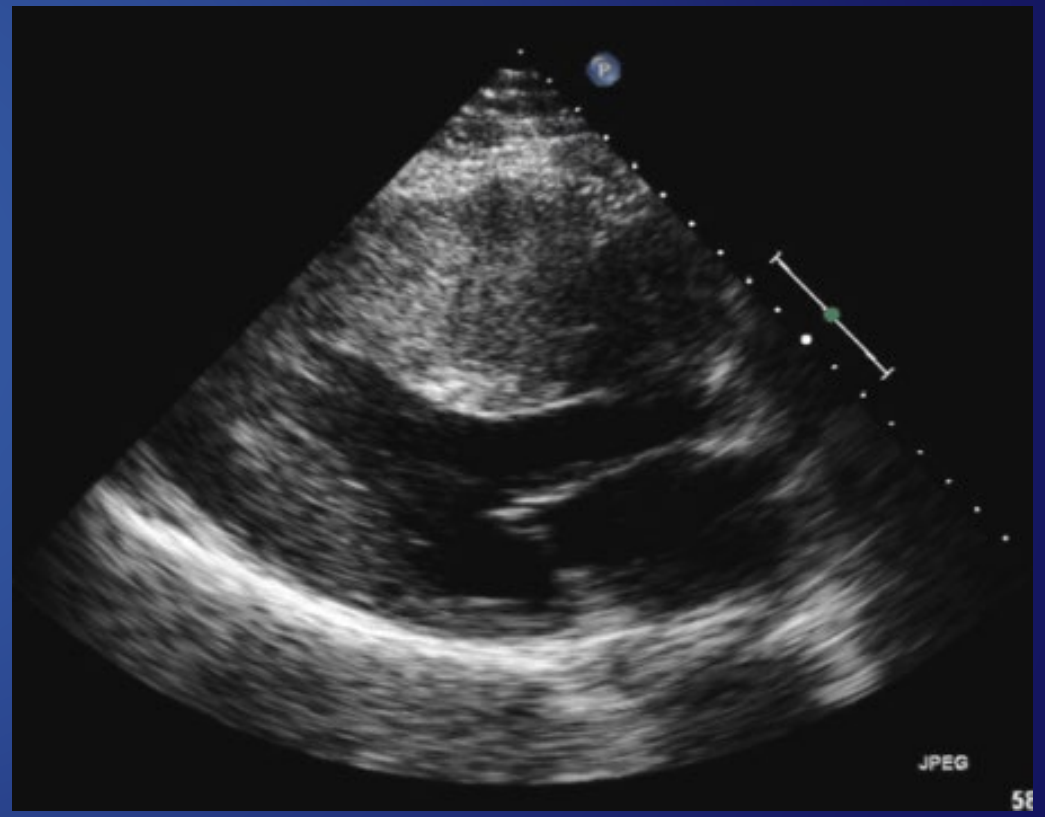


NON-OBSTRUCTED HCM WITH DIASTOLIC HEART FAILURE

- Driven by hypertrophy burden and diastolic dysfunction
- Also occurs with restrictive HCM

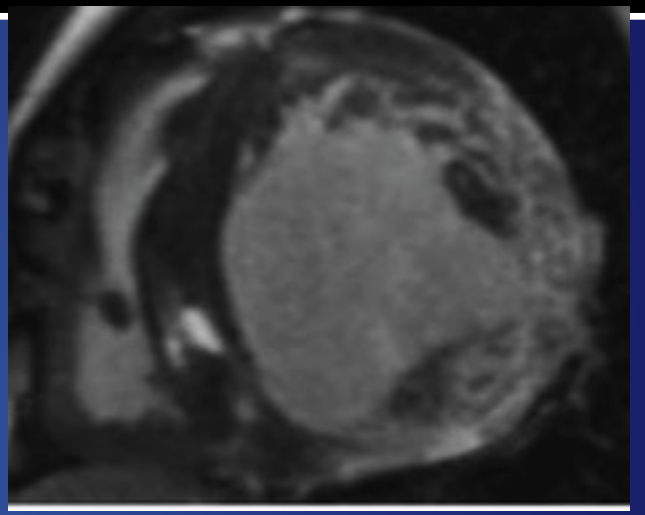
  (especially: thin filament gene mutations)
- Risk factors:
  - Sarcomere mutation, max wall thickness, left atrial enlargement, age of presentation
- Can be precursor to systolic dysfunction

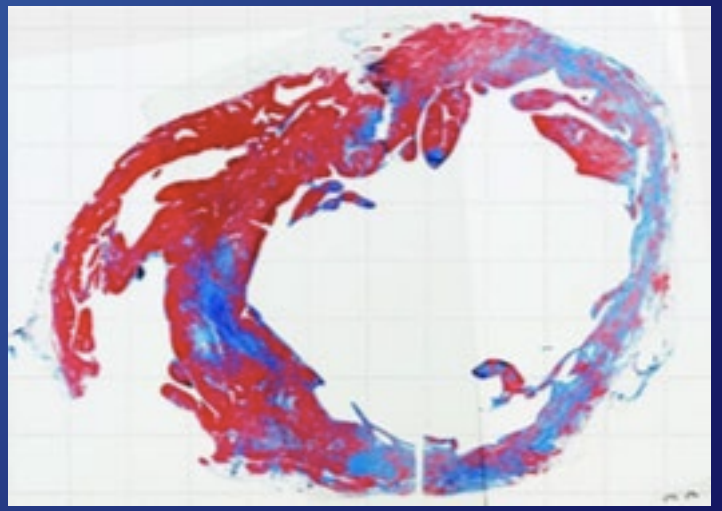
  and/or
- Progress to refractory diastolic/restrictive



"END-STAGE" WITH COMBINED SYSTOLIC / DIASTOLIC HEART FAILURE

- Driven by hypertrophy burden, diastolic dysfunction, microvascular ischemia, and fibrotic remodeling
- Advanced fibrosis leads to relative chamber dilation, systolic dysfunction
- Risk markers: sarcomere mutation, "double" sarcomere mutations, LV dilation, EF ≤55%
- Systolic dysfunction often "mild"
- Prognosis is poor
- If suspected: refer to HF/Transplant Specialist





Funada, et al., *Heart Vessels* 2014

CONCLUSIONS

- For both individual and family risk assessment, HCM should be viewed as 2 separate conditions:

  Genetic/Familial HCM or Non-Familial HCM

- Most familial/genetic cases due to sarcomere gene mutations

  Caveat: small proportion of early onset HCM with negative genetic testing

- Risk of SCD most accurately assessed by combination of ESC risk estimation + MRI + genetics
- Sarcomere mutation HCM is associated with earlier diagnosis and greater cumulative lifetime risk

WHEN TO REFER TO AN HCM CENTER?

- Young HCM patients (age <40)
- Risk factors for heart failure and/or SCD
- LVOT obstruction refractory to medical management
- Cardiac genetic counseling
- Single consults or long-term co-management
- Also evaluate familial DCM, ARVC, inherited arrhythmias