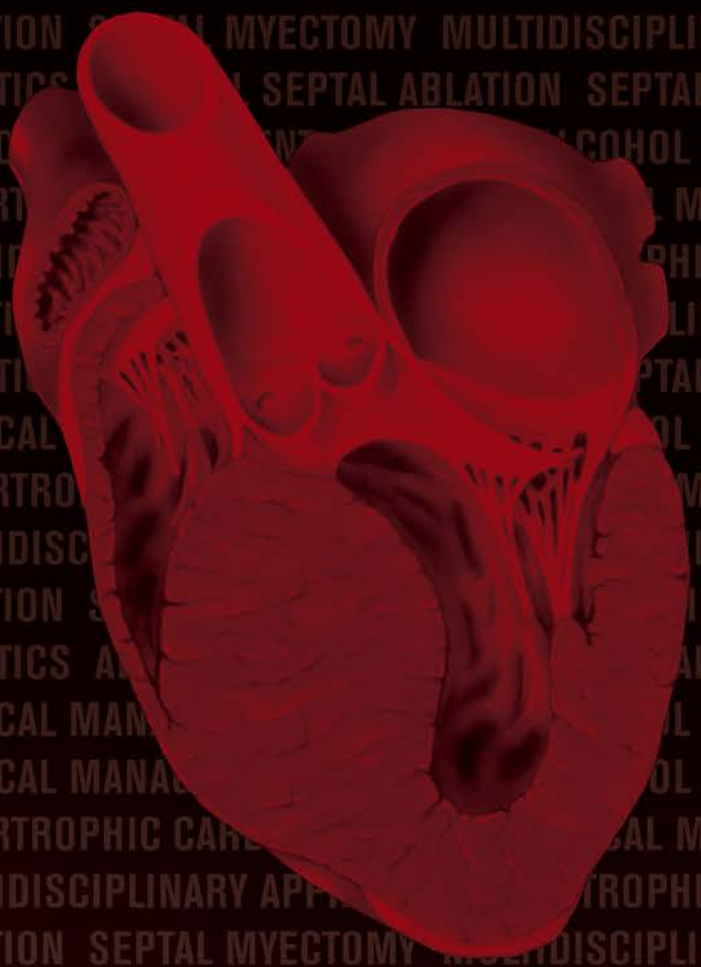

What Clinicians Need to Know About Genetic Testing for Patients and Families with HCM

Sharon Cresci, MD
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Cardiovascular Division
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Saint Louis, MO

Washington University and Barnes-Jewish Heart & Vascular Center

DISCLOSURE

- Dr. Cresci has no relevant financial interests to disclosure

Should I Offer Genetic Testing to my Patient with HCM ???

Genetic Testing – 2 Categories:

- Diagnostic
  - Comprehensive sequence analysis to identify a disease-causing mutation in a patient with HCM
- Predictive
  - Focused genetic testing to determine if a family member has a previously identified mutation
    - Pathogenic or Likely pathogenic mutation has been identified in the index family member who has HCM

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PRACTICE GUIDELINE

2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy

A Report of the American College of Cardiology Foundation/
American Heart Association Task Force on Practice Guidelines

Developed in Collaboration With the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons

Genetic Testing Strategies/Patient Screening—Recommendations

Class:	Screening Guideline:
I	Evaluation of family history and genetic counseling is recommended as part of the assessment of patients with HCM
I	Persons who undergo genetic testing should also undergo counseling by someone knowledgeable in genetics of CV disease
I	Genetic testing is recommended when patients with an atypical clinical presentation of HCM or when another genetic condition is suspected to be the cause of the LVH
I	Screening (clinical with or without genetic testing) is recommended in all 1st degree relatives of patients with HCM
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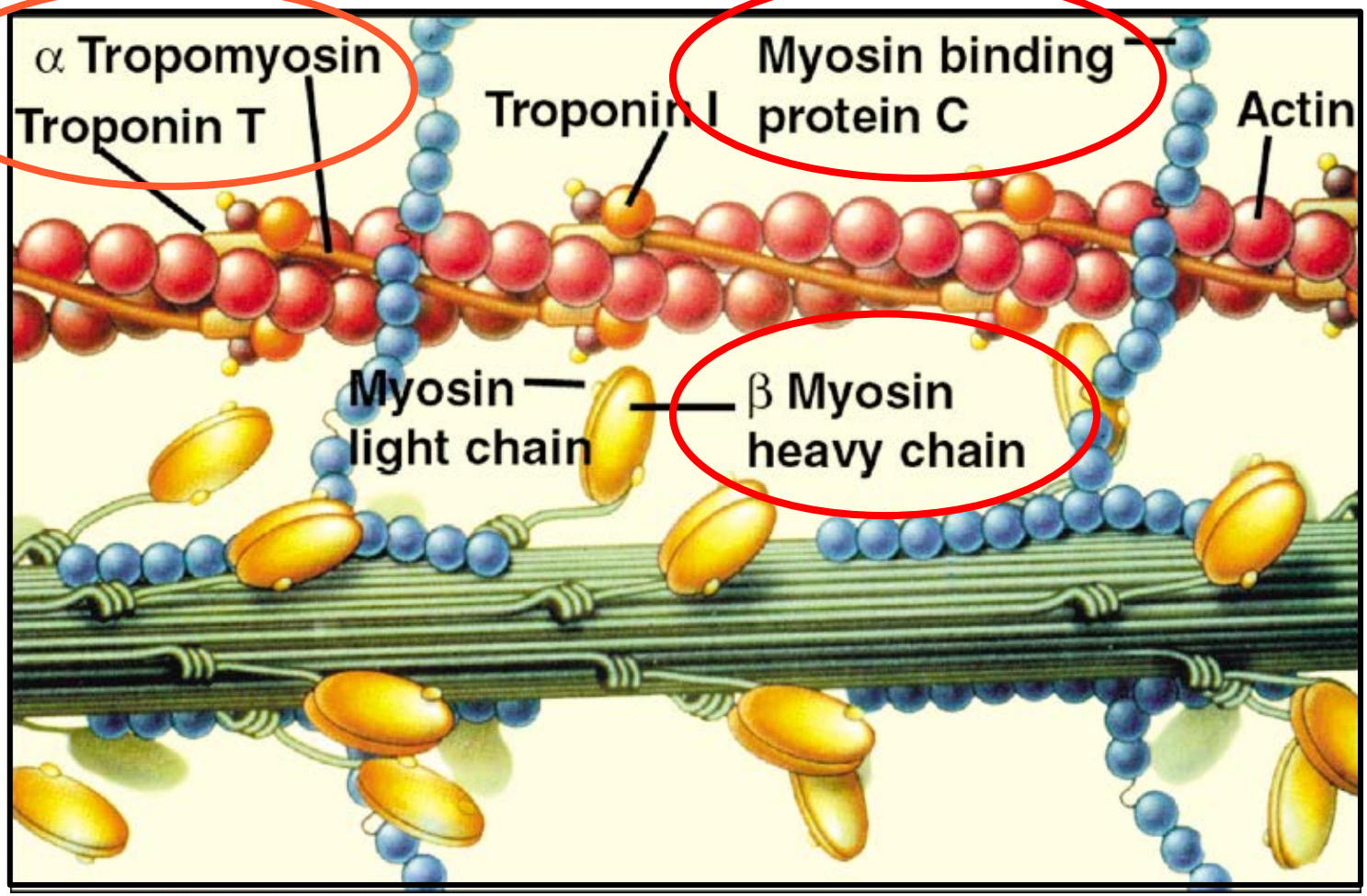
HCM is Caused by More than 1,400 Individual Mutations in More than 11 Genes



Arad M, Seideman JG, Seidman CE. *Hum Mol Genet*, 2002;11:2499-2506

Genetic Testing Strategies/Patient Screening—HCM Phenocopies

Metabolic myocardial storage CMs (≤ 1%)

- Regulatory subunit of adenosine monophosphate-activated protein kinase glycogen storage disease
  - (*PRKAG2*)
- Lysosome-associated membrane protein or Danon disease
  - (*LAMP2*)
  - X-linked dominant
- Fabry (α-galactosidase A deficiency)
  - *(GLA)*
  - X-linked recessive

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Responds to enzyme replacement therapy

Genetic Testing Strategies/Patient Screening—HCM Phenocopies

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Typically rapidly progressive
early consideration for OHT

Genetic Testing Strategies/Patient Screening—HCM Phenocopies

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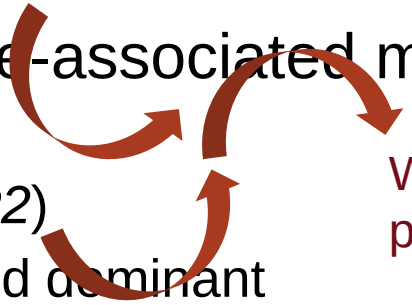

Wolf-Parkinson-White pattern on ECG

Genetic Testing Strategies/Patient Screening—HCM Phenocopies

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Symmetric LVH and late gadolinium enhancement in posterobasal wall on MRI

Genetic Testing – 2 Categories:

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  - Comprehensive sequence analysis to identify a disease-causing mutation in a patient with HCM
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    - Pathogenic or Likely pathogenic mutation has been identified in the index family member who has HCM

Genetic Testing Strategies/Patient Screening—Atypical Presentation of HCM

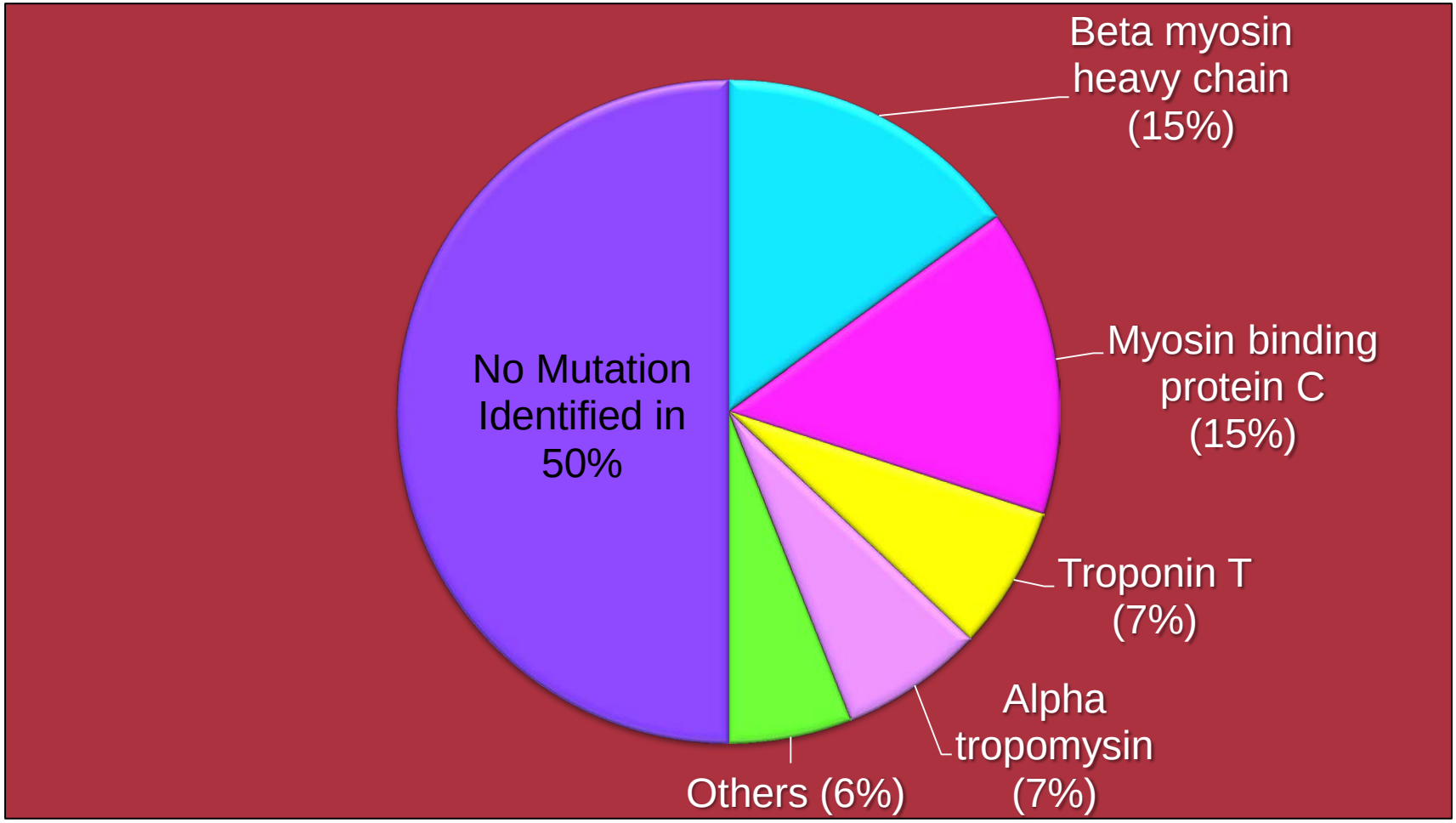
- Can also help to discriminate between HCM and other causes of LVH, including HTN and “athlete’s heart”
  - Only helpful if pathogenic or likely pathogenic mutation is found

Proposed Classification System for Sequence Variants Identified by Genetic Testing:

Class	Description	Probability of being Pathogenic
5	Definitely Pathogenic	> 0.99
4	Likely Pathogenic	0.95-0.99
3	Uncertain (Variant of Unknown Significance; VUS)	0.05-0.949
2	Likely Not Pathogenic or of Little Clinical Significance	0.001-0.049
1	Not Pathogenic or of No Clinical Significance	<0.001

Plon SE, Eccles CM et al. *Hum Mutat.* 2008; 29: 1282-1291.

Proposed Classification System for Sequence Variants Identified by Genetic Testing:



Human Molecular Genetics, 2002, Vol. 11, No. 20

Genetic Testing Strategies/Patient Screening—Atypical Presentation of HCM

- Can also help to discriminate between HCM and other causes of LVH, including HTN and “athlete’s heart”
  - Only helpful if pathogenic or likely pathogenic mutation is found
  - No pathogenic mutation or VUS found → can NOT conclude that the patient does not have HCM—still left with clinical impression and uncertain about recommendations for family members

Genetic Testing – 2 Categories:

- Diagnostic
  - Comprehensive sequence analysis to identify a disease-causing mutation in a patient with HCM

- Predictive
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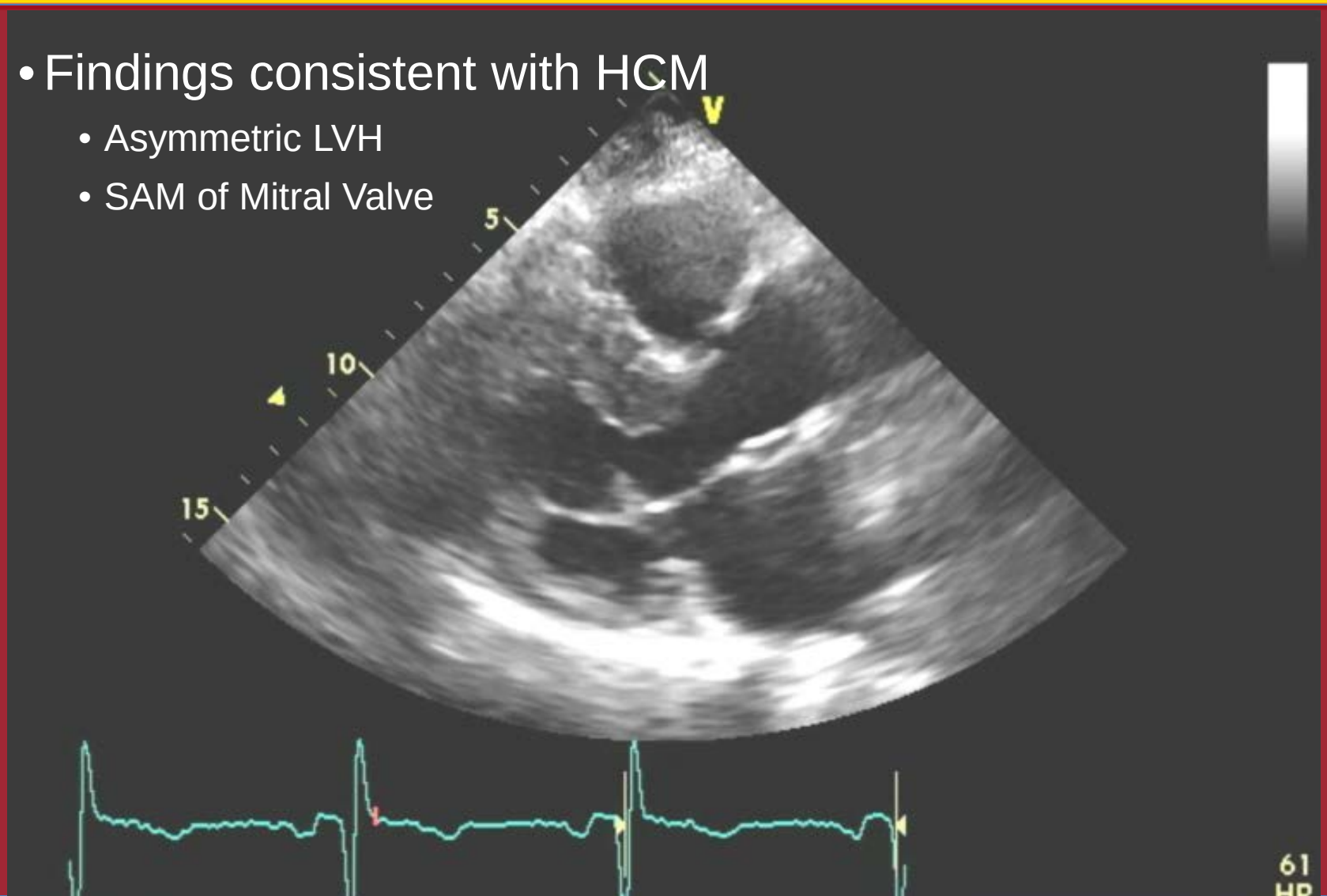
Clinical Screening with Echocardiography (& 12-Lead ECG) for Detection of HCM

Age:	Screening Guideline:
<12 yrs	Optional unless any of the following are present: ➢ Family history of early HCM-related death, early development of LVH, or other adverse complications ➢ Competitive athlete in intense training program ➢ Symptoms ➢ Other clinical findings that suggest early LVH
12-18 yrs	Every 12-18 months
>18-21 yrs	Every ≤5 years or w/onset of symptoms or w/change in symptoms ➢ More frequently if there is a family history of late-onset LVH or HCM-related complications

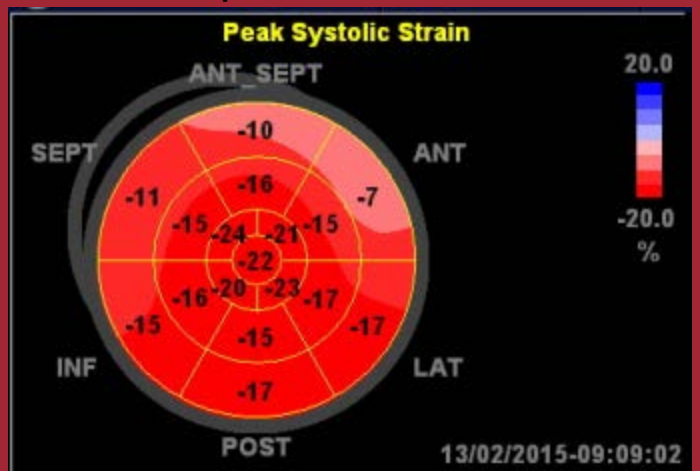
Clinical Screening with Echocardiography for Detection of HCM

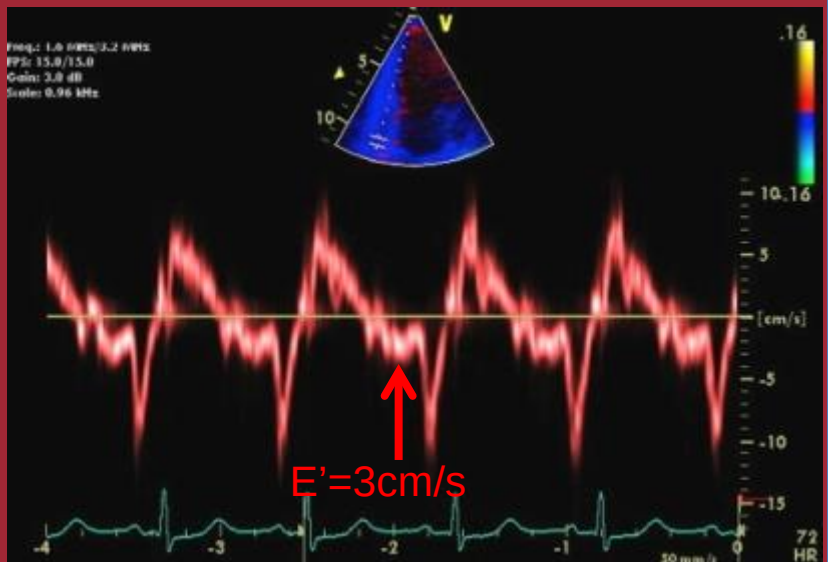
- Findings consistent with HCM
  - Asymmetric LVH
  - SAM of Mitral Valve



Clinical Screening with Echocardiography for Detection of HCM

- Findings consistent with HCM
  - Asymmetric LVH
  - SAM of Mitral Valve
- Subtle findings
  - Abnormal tissue Doppler pattern for age
  - Abnormal peak systolic strain
  - Crescent shape of LV

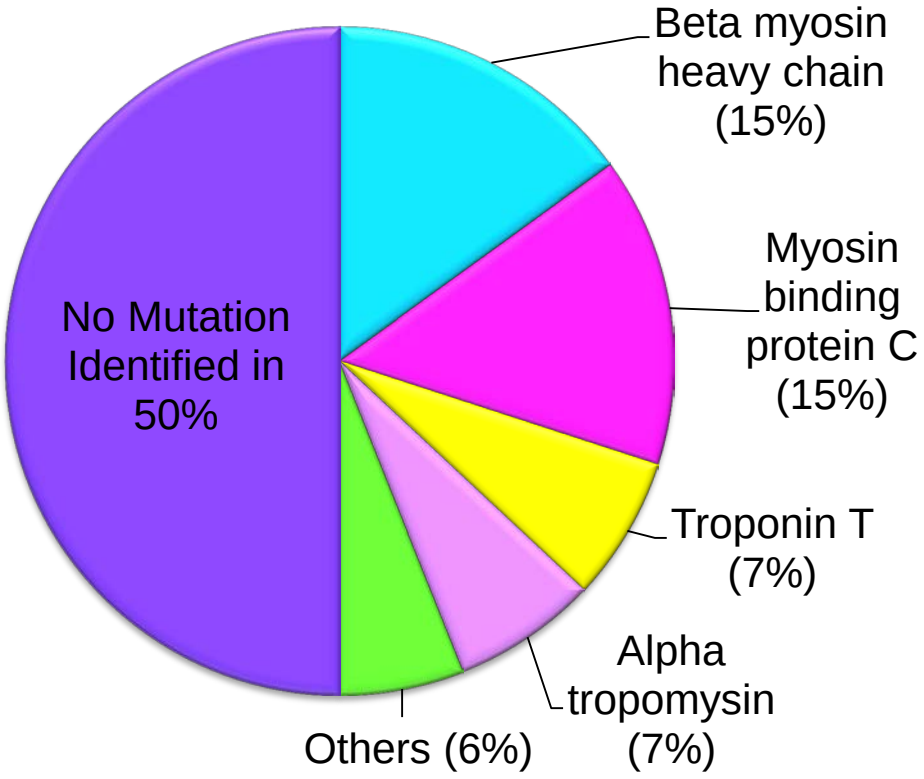




Genetic Testing Strategies/Family Screening—Recommendations

Identify Family Member with Phenotype (who is willing to be tested)

No Pathogenic variant identified



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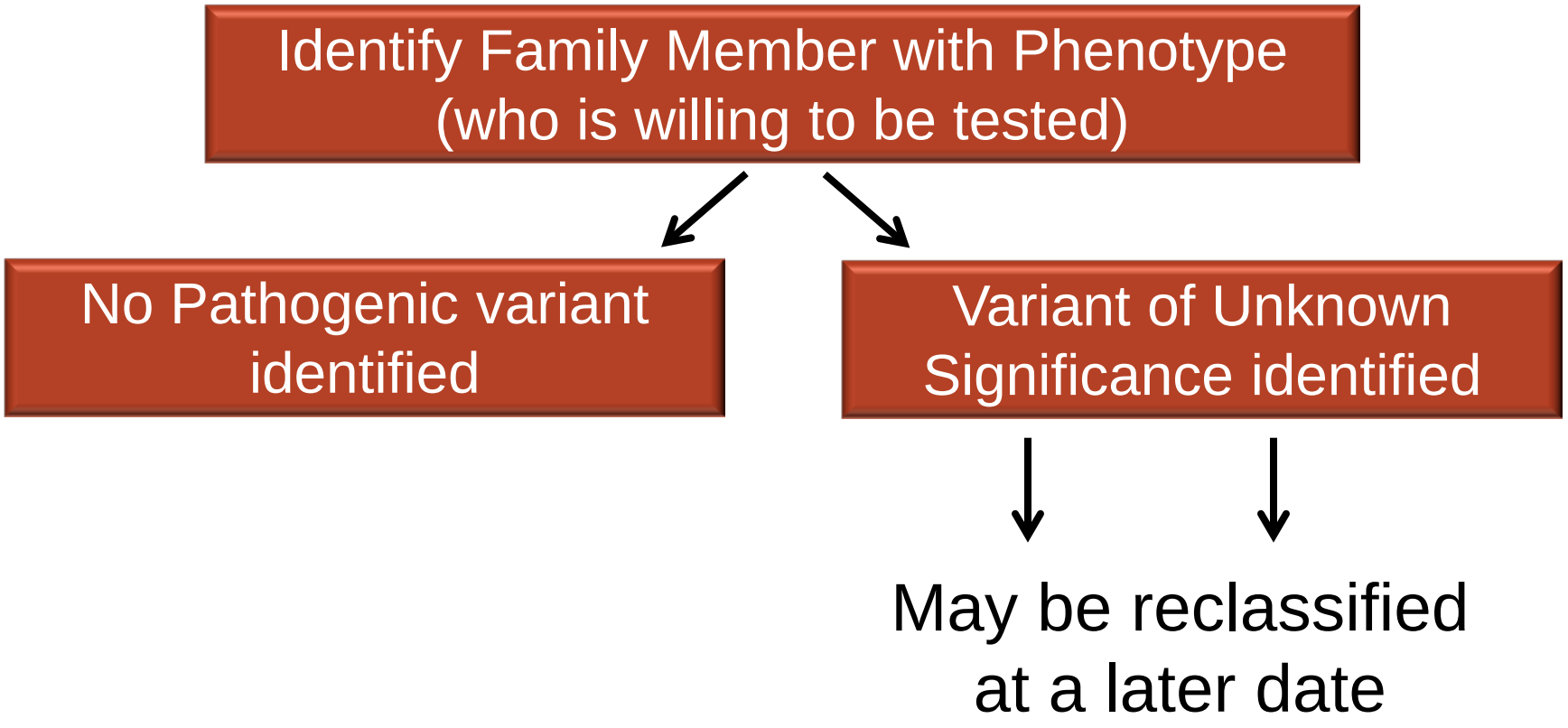

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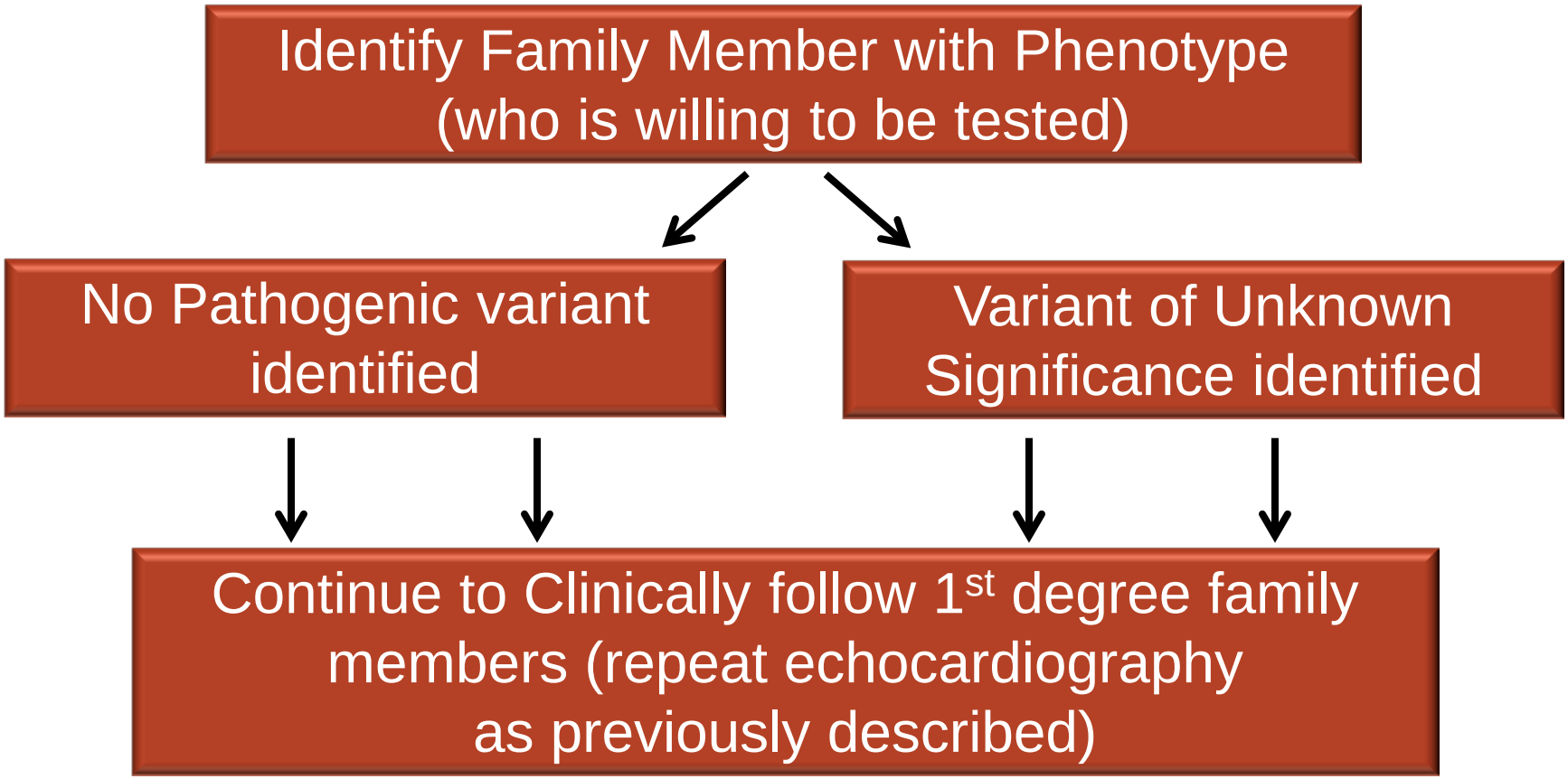

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Class:	Screening Guideline:
IIb	The usefulness of genetic testing in the assessment of risk of SCD in HCM is uncertain
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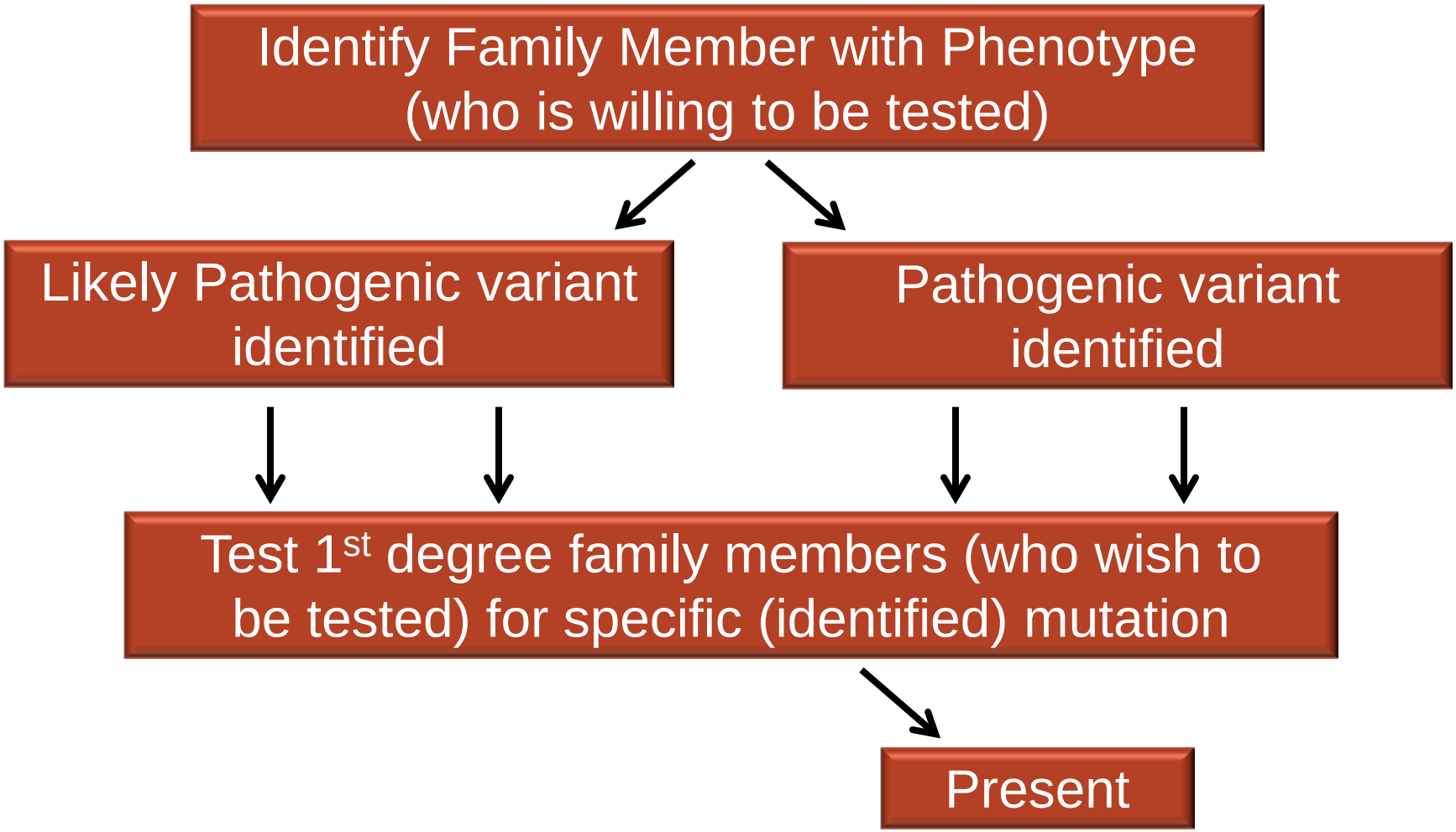
Genetic Testing Strategies/Family Screening—Recommendations

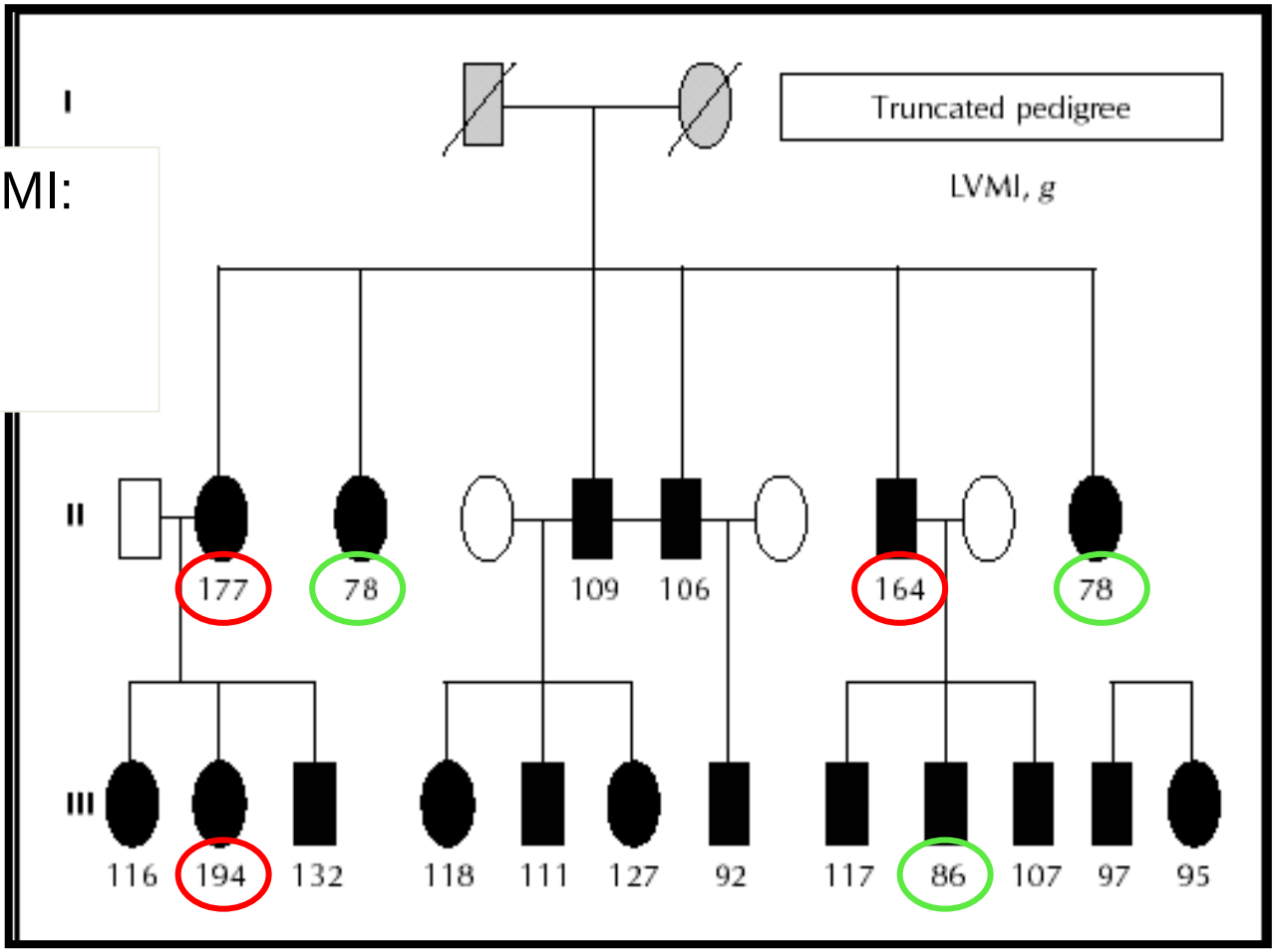


Genetic Testing Strategies/Family Screening—Recommendations

Normal LVMI:

≤115 in ♀

≤95 in ♂

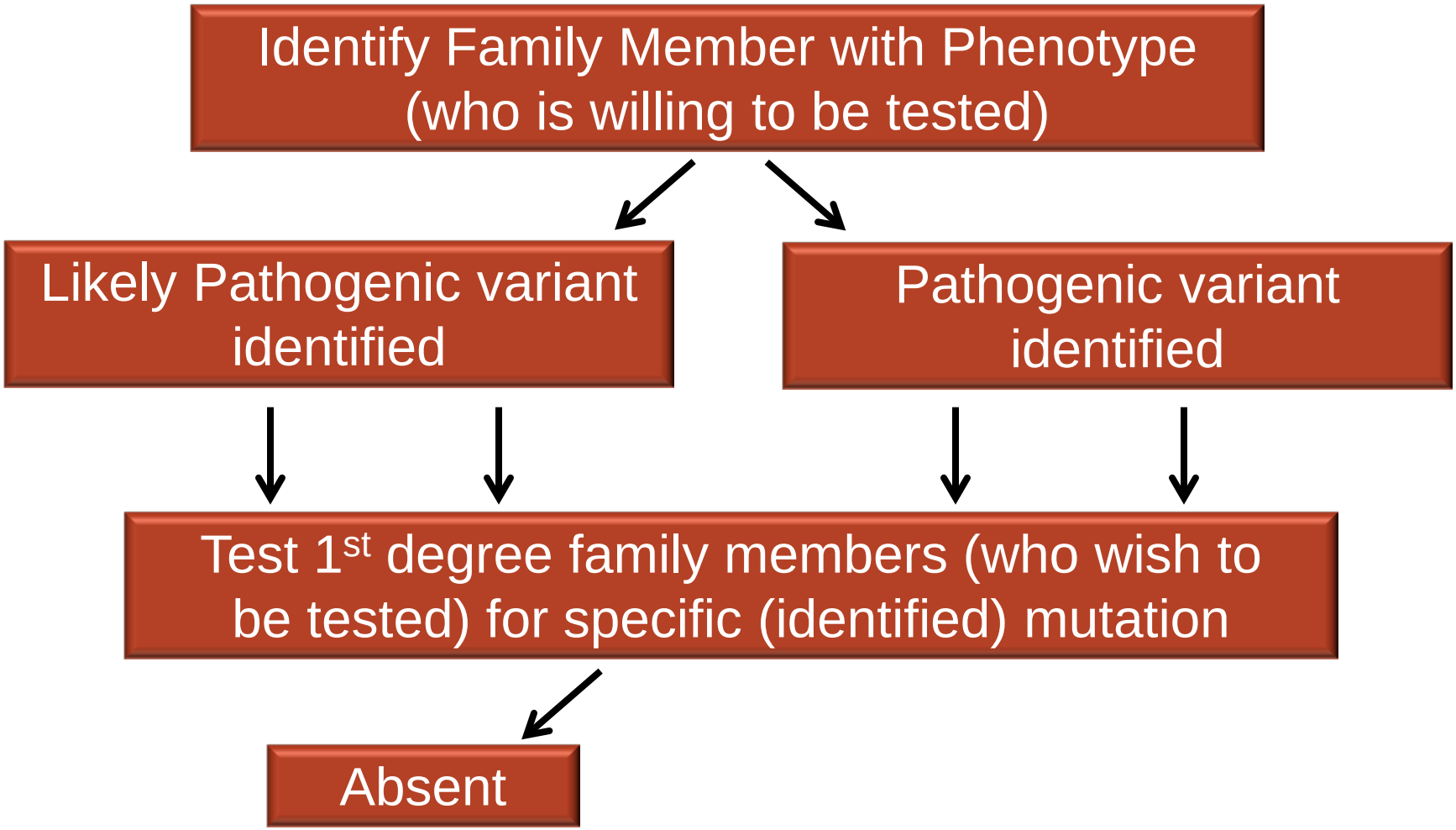


Marian AJ. *Curr Opin Cardiol*, 2002;17:242-252.

Genetic Testing Strategies/Family Screening—Issues

- Incomplete Penetrance
  - Even if M (+), may always be P (-)

Genetic Testing Strategies/Family Screening—Recommendations



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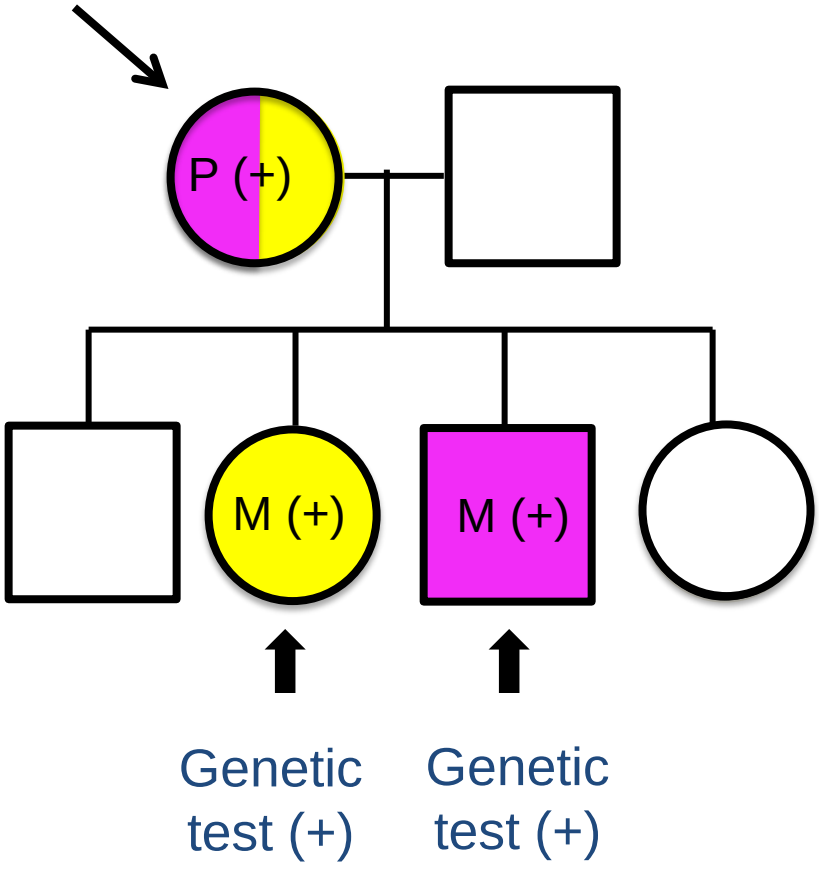
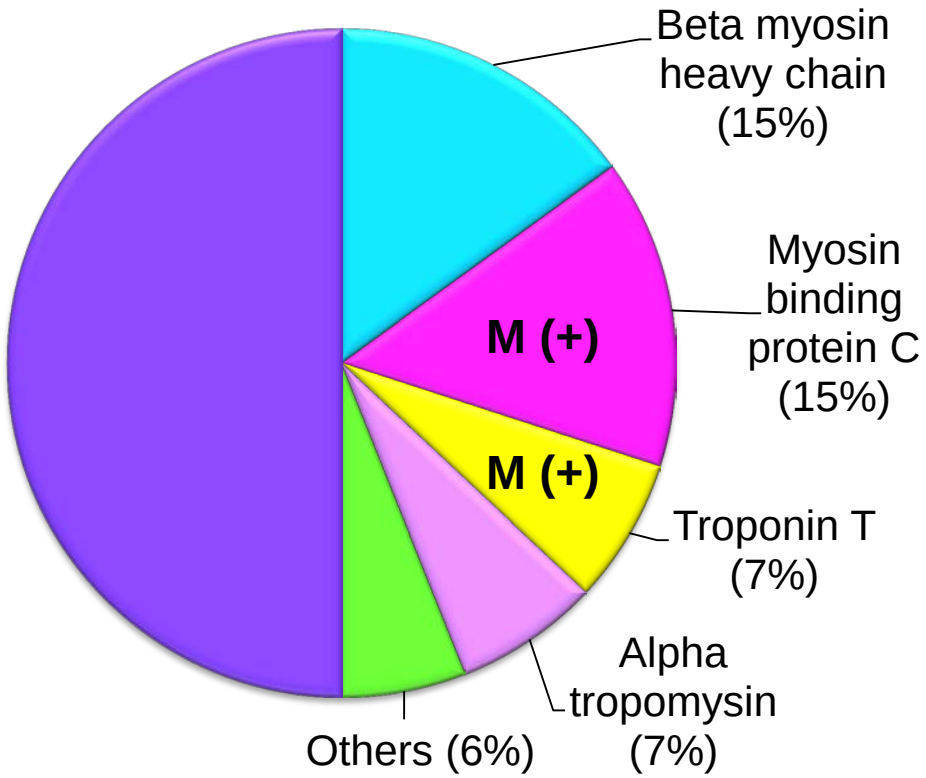
Genetic Testing Strategies/Family Screening—Issues

- Double mutations are present in 5-8% of patients with HCM

Marziliano N *et al. Neonatology*, 2012: 102:254-258.
Ingles J *et al*. *J Med Genet* 2005:42:e59

Genetic Testing Strategies/Family Screening—Issues





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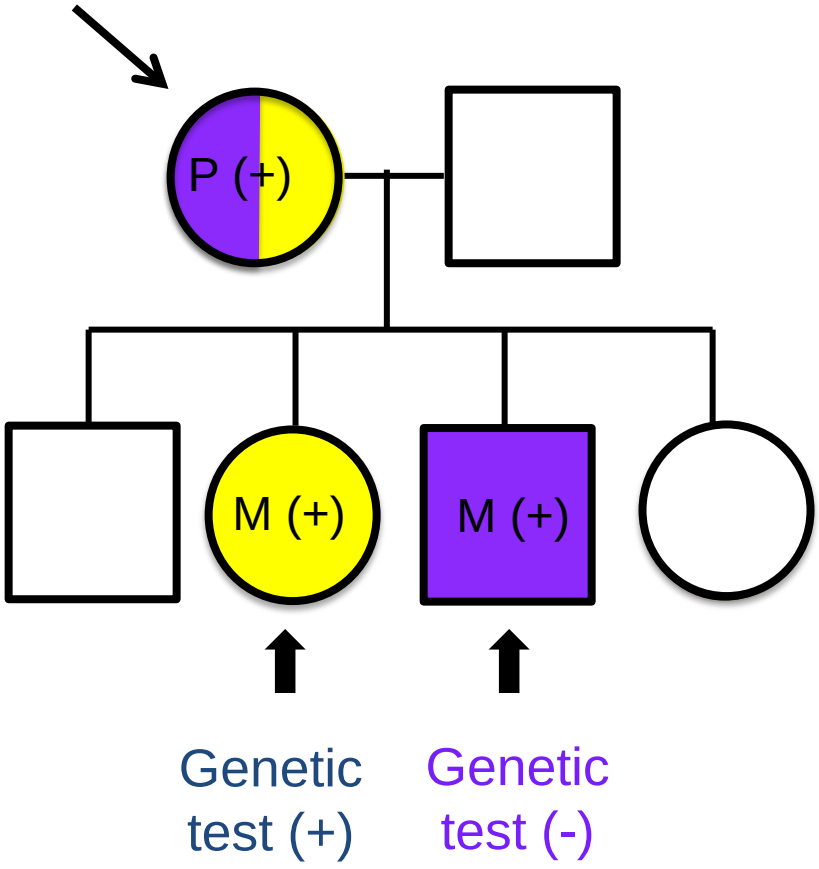

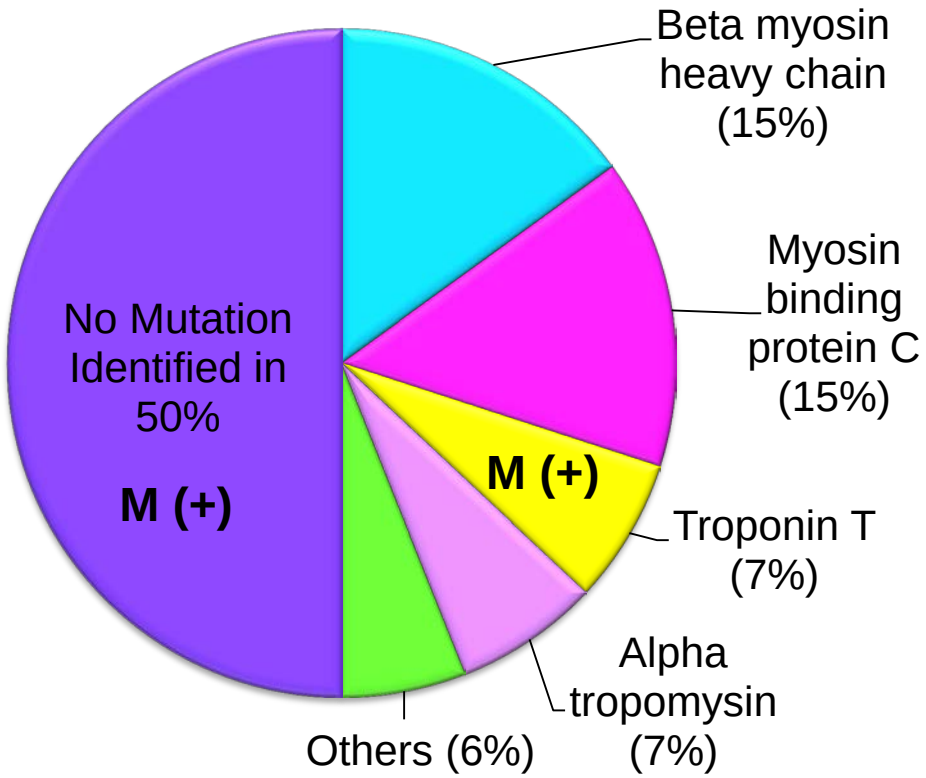

Human Molecular Genetics, 2002, Vol. 11, No. 20

Genetic Testing Strategies/Family Screening—Issues

- Incomplete Penetrance
  - Even if M (+), may always be P (-)
- Double Mutations
  - If M (-), there is a minimal, but not 0%, chance of being P (+)

Double or compound sarcomere mutations in hypertrophic cardiomyopathy: A potential link to sudden death in the absence of conventional risk factors

Barry J. Maron, MD,* Martin S. Maron, MD,† Christopher Semsarian, MB, BS, PhD‡

*From the *Hypertrophic Cardiomyopathy Center, Minneapolis Heart Institute Foundation, Minn*
†Hypertrophic Cardiomyopathy Center, Tufts Medical Center, Boston, Maryland; and ‡Agnes C
Molecular Cardiology, Centenary Institute, Sydney Medical School, University of Sydney and
Royal Prince Alfred Hospital, Camperdown, Australia.

BACKGROUND Risk stratification strategies employing sarcomere gene mutational analysis have proved imprecise in identifying high-risk patients with hypertrophic cardiomyopathy (HCM). Therefore, additional genetic risk markers that reliably determine which patients are predisposed to sudden death are needed.

OBJECTIVE The objective of this study was to determine whether multiple disease-causing sarcomere mutations can be regarded as markers for sudden death in the absence of other conventional risk factors.

METHODS Databases of 3 HCM centers were accessed, and 18 disease-causing mutations in genes encoding

tation independently from each of his parents
MYBPC3 and *TNNI3* mutations and compou
predisposing clinical markers evide
cardiac event.

Neonatology

Short Communication

Neonatology 2012;102:254–258
DOI: 10.1159/000339847

A Case of Compound Mutations in the *MYBPC3* Gene Associated with Biventricular Hypertrophy and Neonatal Death

Nicola Marziliano[a, c] Piera Angelica Merlini[b] Gabriele Vignati[b]
Francesco Orsini[a] Valentina Motta[a] Laura Bandiera[a] Mariano Intrieri[c]
Silvio Veronese[a]
[a]Pathology Department and [b]Cardiovascular Department, AO Ospedale Cà Granda Niguarda, Milan, and
[c]Health Sciences Department, Faculty of Medicine, University of Molise, Campobasso, Italy

ORIGINAL ARTICLE

Hypertrophic cardiomyopathy family with double-heterozygous mutations; does disease severity suggest double-heterozygosity?

ELECTRONIC LETTER

Compound and double mutations in patients with hypertrophic cardiomyopathy: implications for genetic testing and counselling

J Ingles, A Doolan, C Chiu, J Seidman, C Seidman, C Semsarian

J Med Genet 2005;**42**:e59 (http://www.jmedgenet.com/cgi/content/full/42/10/e59). doi: 10.1136/jmg.2005.033886

gen, J.F. Hermans-van Ast, Y.H.J.M. Arens, S.M. Schalla, C.E.M de Die-Smulders
ard, Y.M. Pinto

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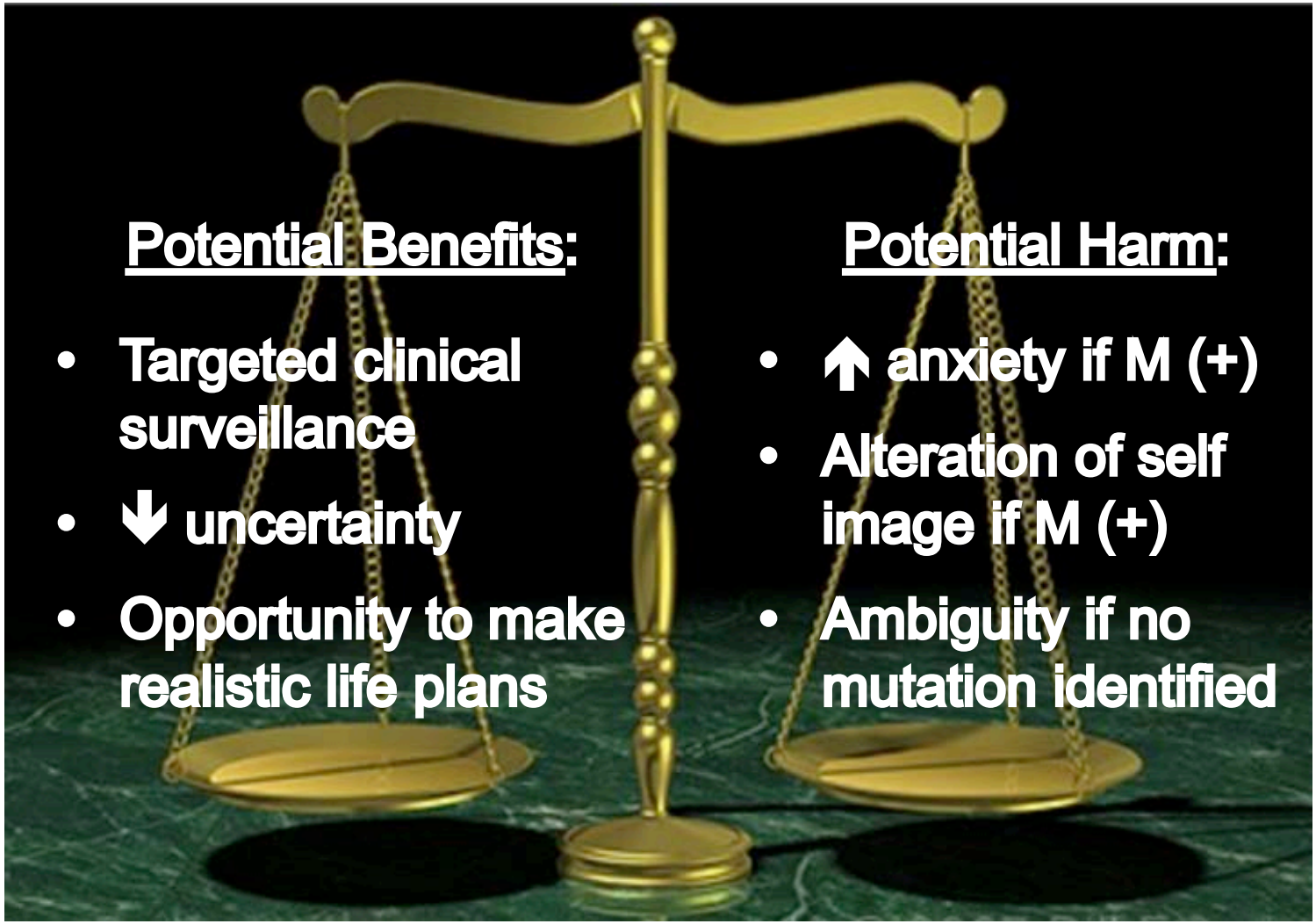
Genetic Testing—A Personal Decision



Heart & Vascular Center

BARNES-JEWISH Hospital
BJC HealthCare

Washington University in St. Louis
Physicians

NATIONAL LEADERS IN MEDICINE