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Genetic Testing in Cardiomyopathies

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Outline

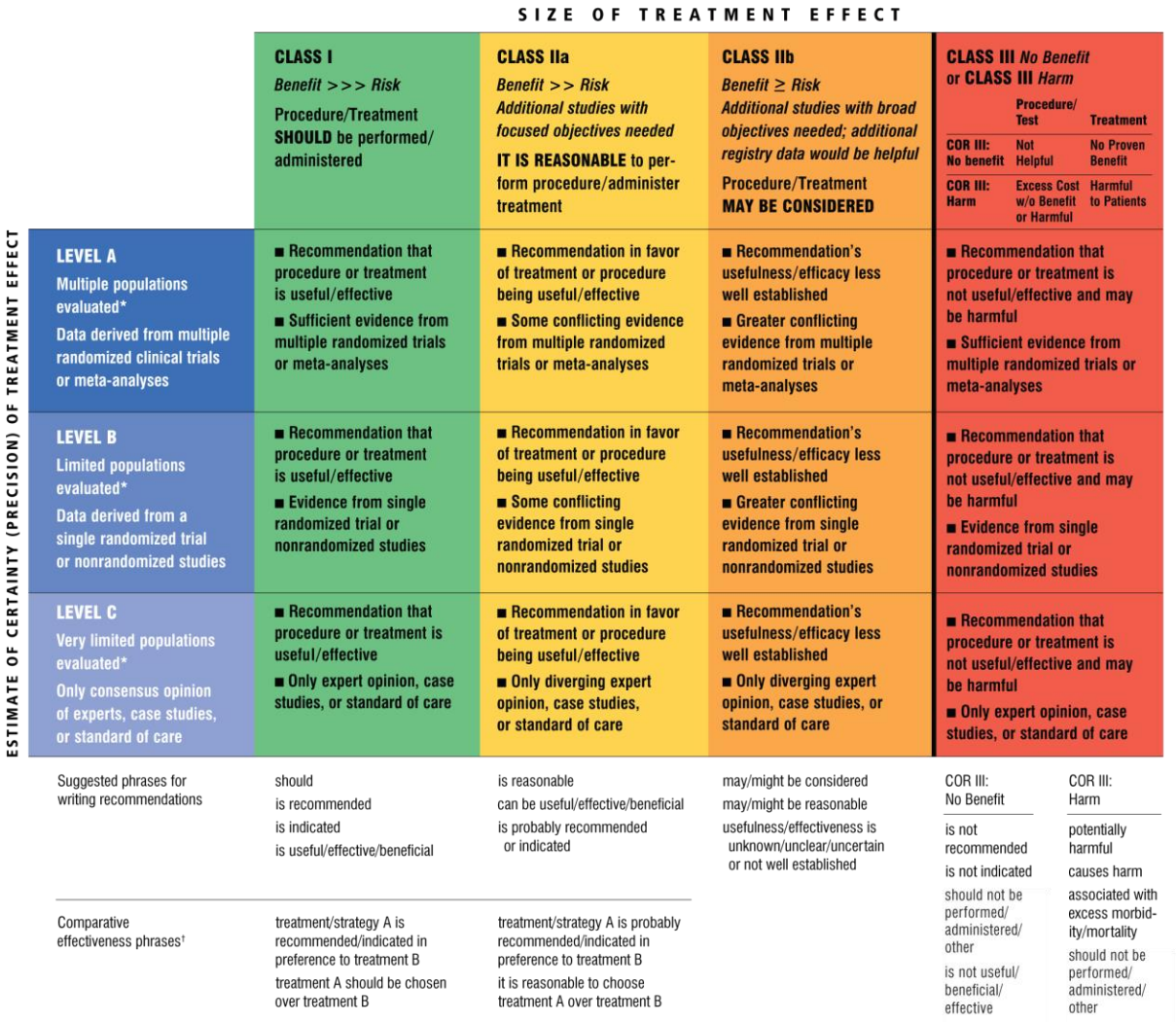
Determine appropriate patients to perform genetic testing in patients with Hypertrophic Cardiomyopathy.

Determine appropriate testing of relatives of patients with HCM

Determine appropriateness to perform genetic testing in patients with ARVD

Determine appropriate genetic testing of patients with Dilated cardiomyopathy and when to utilize such testing

Classification of Recommendations and Levels of Evidence



SIZE OF TREATMENT EFFECT

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT

	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* Procedure/ Test / Treatment COR III: No benefit — Not Helpful / No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful / Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit: is not recommended; is not indicated; should not be performed/ administered/ other; is not useful/ beneficial/ effective COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/ efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

Genetic Testing Strategies/Family Screening in HCM

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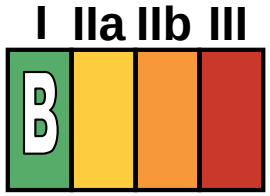
Genetic Testing Strategies/Family Screening

Evaluation of familial inheritance and genetic counseling is recommended as part of the assessment of patients with HCM.

Patients who undergo genetic testing should also undergo counseling by someone knowledgeable in the genetics of cardiovascular disease so that results and their clinical significance can be appropriately reviewed with the patient.

Screening (clinical, with or without genetic testing) is recommended in first-degree relatives of patients with HCM.



Genetic testing for HCM and other genetic causes of unexplained cardiac hypertrophy is recommended in patients with an atypical clinical presentation of HCM or when another genetic condition is suspected to be the cause.

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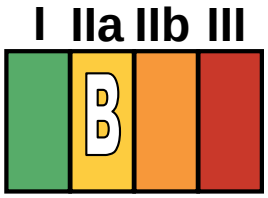
Genetic Testing Strategies/Family Screening



Genetic testing is reasonable in the index patient to facilitate the identification of first-degree family members at risk for developing HCM.

The usefulness of genetic testing in the assessment of risk of SCD in HCM is uncertain.

Genetic Testing Strategies/Family Screening

No Benefit

Genetic testing is not indicated in relatives when the index patient does not have a definitive pathogenic mutation.

No Benefit

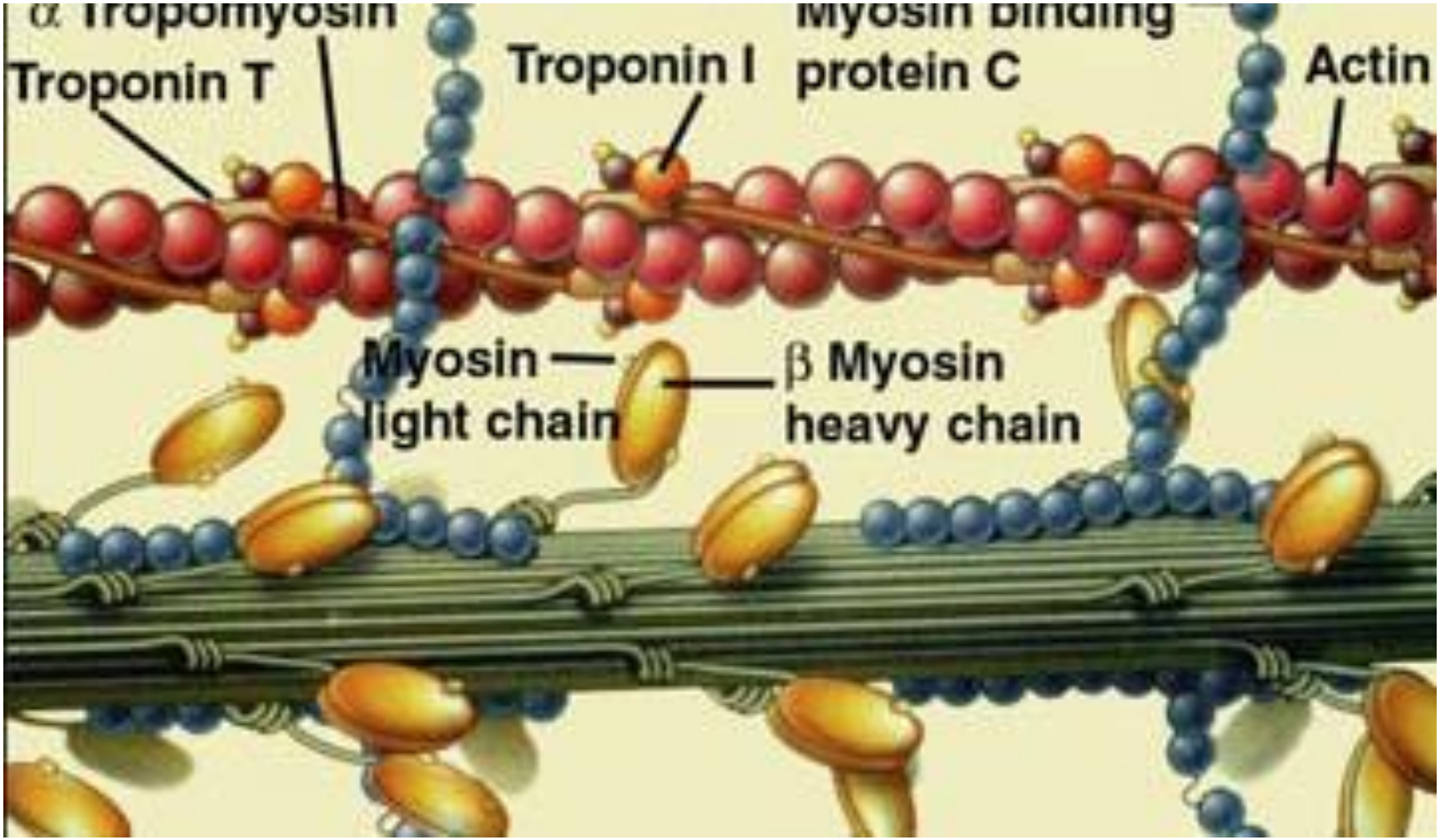
Ongoing clinical screening is not indicated in genotypenegative relatives in families with HCM.

Genotype-Positive/Phenotype-Negative Patients

Genotype-Positive/Phenotype-Negative Patients

In individuals with pathogenic mutations who do not express the HCM phenotype, it is recommended to perform serial ECG, TTE, and clinical assessment at periodic intervals (12 to 18 months in children and adolescents and about every 5 years in adults), based on the patient's age and change in clinical status.

HCM is a disease of Sarcomeres



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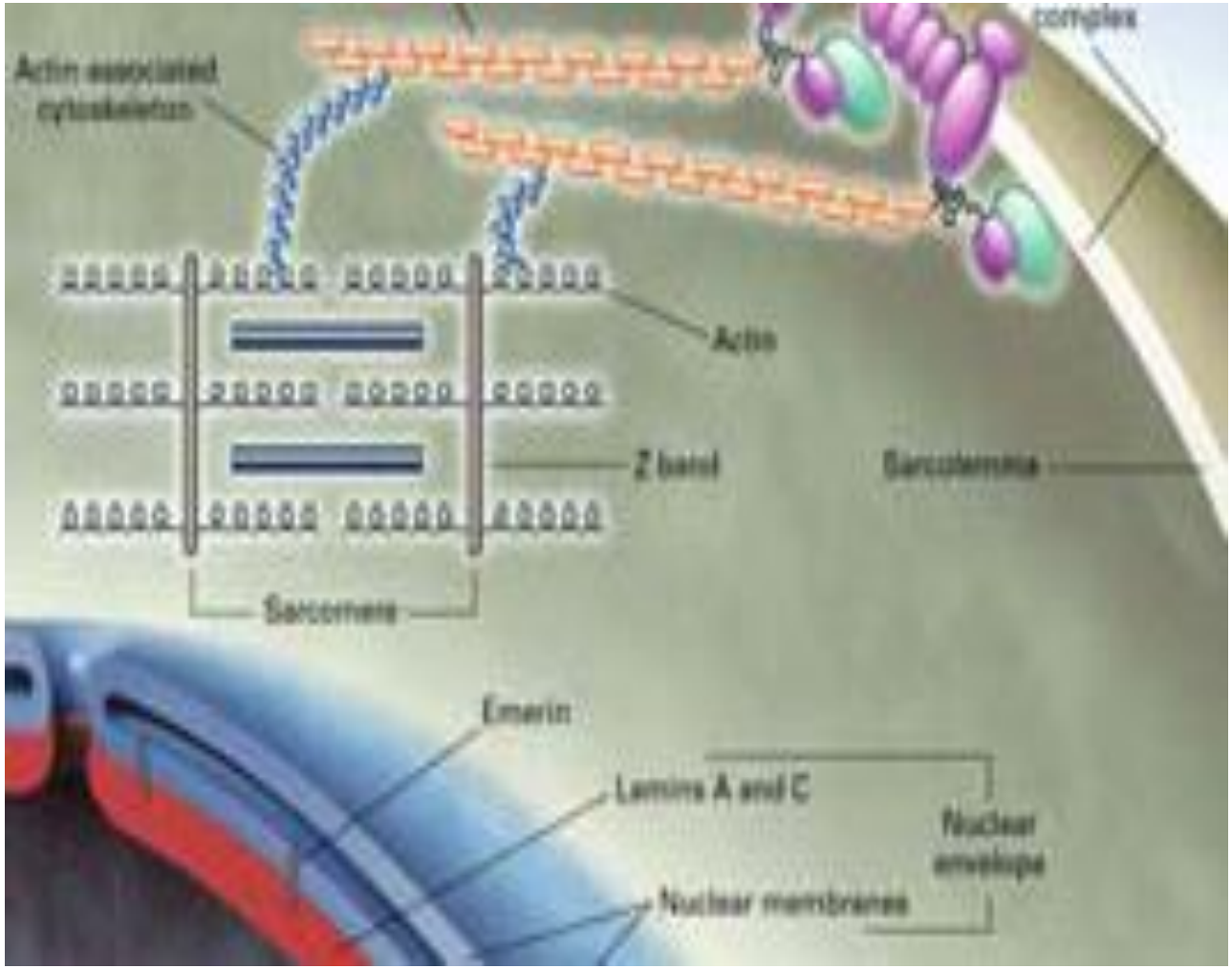
Genetic causes of Dilated Cardiomyopathy



60+ putative loci and genes associated with DCM

- **Encode sarcomere, nuclear envelope, cytoskeletal proteins**
- **Gene mutations identified in 40% of familial DCM**

MacRae C. JACC 2009;54:942
Hershberger R. CTS 2008;2008:1:21
Taylor M et al. JACC 2003;41:771-80.

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Familial DCM

Inheritance

– autosomal dominant DCM : majority

– autosomal recessive DCM : ~16%, younger age of onset, more rapid progression to death or transplant

– X-linked DCM: ~10%, males with severe progressive HF related to dystrophin mutations

- **Patterns**

– With or without conduction system disease

– With or without skeletal myopathy

Mestroni, et al. JACC 1999; 34: 181.

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DCM without conduction system disease

- Most common phenotype
- Mutations in sarcomere proteins account for up to 30% of familial DCM
- Different mutations in these same genes cause HCM
- Titin (TTN) truncations most common in DCM
  - Key component of sarcomeric force generation
  - present in up to 20% of idiopathic DCM (higher prevalence in familial DCM)
  - Can be detected in 2-3% of phenotypically normal patients
  - Men carry worse prognosis than women

Japp, et al. JACC 2016; 67: 2996-3010

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Other Familial DCM Phenotypes

- **X-linked DCM**
  - **DystrophinMutations**
- **Duchenne Muscular Dystrophy**
  - **Proximal muscle weakness, DCM, SVT, and AV nodal disease**
  - **Extensive fibrosis of posterobasal LV wall**
  - **Tall right precordial R waves, deep Q waves in I, aVL, V5-V6**
- **Becker Muscular Dystrophy**
  - **Milder skeletal muscle symptoms, but cardiac involvement more evident**
  - **Biventricular failure, infranodal conduction abnormalities/heart block common**
- **Cardiomyopathy and sensorineural hearing loss**
  - **Mitochondrial gene mutations (matrilineal inheritance, e.g. MERRF syndrome)**

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Left Ventricular Non-Compaction

- **Possibly Inherited, but low screening efficiency for genetic testing**

- **Current literature suggests increased risk for LV dilation and CHF**

- **Possible increased risk for SCD**

- **Current recommendations suggest no competitive athletics**

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Arrythmogenic Right Ventricular Dysplasia (ARVD)

- A type of nonischemic cardiomyopathy that involves primarily the right ventricle.

- It is characterized by hypokinetic areas involving the free wall of the right ventricle, with fibrofatty replacement of the right ventricular myocardium, with associated arrhythmias originating in the right ventricle

- ARVD is caused by genetic defects of the parts of myocardium known as desmosomes, areas on the surface of heart muscle cells which link the cells together. The desmosomes are composed of several proteins, and many of those proteins can have harmful mutations.

Genetics of ARVD

- Genetic cardiomyopathy
- Primarily autosomal dominant
- 30-60% are due to mutations in one of the desmosomal genes
- Can get compound or digenic heterozygosity
- Incomplete penetrance (20-30%)
- Variable and age-dependent expression
- 20-30% cases have a family history

Marcus et al. JACC 2013;61:1945-8.

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Natural History of ARVD

- Typically present from teens to 40s
- Prevalence: 1:5000
- Male:Female: 3:1
- Natural History: 4 phases of disease
- Concealed – asymptomatic but increased risk of SCD
- Overt – symptomatic arrhythmias
- Signs and symptoms of RV failure
- Biventricular heart failure ± arrhythmias

Hulot Circulation 2004;110:1879-84.

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Screening Recommendations for 1st Degree Relatives of patients with ARVD

Screening Tests including:

Detailed history with attention to HF, arrhythmias, presyncope or syncope;

Detailed Physical exam

ECG/SAECG

Echocardiogram

cMRI

24 hour Holter

Screening should occur:

Annually between ages 10 and 50 yrs for asymptomatic patients who are genotype + or clinical screening +

Every 3-5 yrs after age 10 for asymptomatic patients who have no genotype identified

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